

---

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

---

SCHEDULE 13D

---

Under the Securities Exchange Act of 1934  
(Amendment No. \_\_)\*

**Sienna Biopharmaceuticals, Inc.**

---

(Name of Issuer)

**Common Stock, \$0.0001 par value**

---

(Title of Class of Securities)

**82622H108**

---

(CUSIP Number)

**Mark McDonnell  
ARCH Venture Corporation  
8755 W. Higgins Road Suite 1025  
Chicago, IL 60631**

---

(Name, Address and Telephone Number of Person Authorized to Receive Notices and Communications)

**February 22, 2019**

---

(Date of Event which Requires Filing of this Statement)

If the filing person has previously filed a statement on Schedule 13G to report the acquisition that is the subject of this Schedule 13D, and is filing this schedule because of §§240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box.

**Note:** Schedules filed in paper format shall include a signed original and five copies of the schedule, including all exhibits. See §240.13d-7 for other parties to whom copies are to be sent.

\*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 disclosures provided in a prior cover page.

The information required on 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).

**Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number.**

---

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Fund VIII, L.P.	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	SEC USE ONLY	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> WC	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> PN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Fund VIII Overage, L.P.	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> WC	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> PN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Partners VIII, L.P.	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> PN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Partners VIII, LLC	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> OO	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Fund X Overage, L.P.	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> WC	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> PN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Partners X Overage, L.P.	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> PN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> ARCH Venture Partners X, LLC	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> Delaware	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> OO	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> Kristina Burow	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> United States	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 11,982 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 11,982 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,810,850 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> IN	

<b>1</b>	<b>NAMES OF REPORTING PERSONS</b> <b>I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)</b> Steven Gillis	
<b>2</b>	<b>CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP</b> (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
<b>3</b>	<b>SEC USE ONLY</b>	
<b>4</b>	<b>SOURCE OF FUNDS (SEE INSTRUCTIONS)</b> AF	
<b>5</b>	<b>CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(D) OR 2(E)</b> <input type="checkbox"/>	
<b>6</b>	<b>CITIZENSHIP OR PLACE OF ORGANIZATION</b> United States	
<b>NUMBER OF SHARES          BENEFICIALLY          OWNED BY EACH          REPORTING PERSON          WITH</b>	<b>7</b>	<b>SOLE VOTING POWER</b> 0 shares
	<b>8</b>	<b>SHARED VOTING POWER</b> 5,798,868 shares
	<b>9</b>	<b>SOLE DISPOSITIVE POWER</b> 0 shares
	<b>10</b>	<b>SHARED DISPOSITIVE POWER</b> 5,798,868 shares
<b>11</b>	<b>AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON</b> 5,798,868 shares	
<b>12</b>	<b>CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS)</b> <input type="checkbox"/>	
<b>13</b>	<b>PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)</b> 19.9%	
<b>14</b>	<b>TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)</b> IN	

## Schedule 13D

**Item 1. Security and Issuer.**

This statement relates to the Common Stock, \$0.0001 par value per share (the "Common Stock"), of Sienna Biopharmaceuticals, Inc. (the "Issuer") having its principal executive office at 30699 Russell Ranch Road, Suite 140, Westlake Village, CA 91362.

**Item 2. Identity and Background.**

- (a) This statement is being filed by (1) ARCH Venture Fund X Overage, L.P. ("AVF X Overage"), (2) ARCH Venture Partners X Overage, L.P. ("AVP X GP"), which is the sole general partner of AVF X Overage, (3) ARCH Venture Partners X, LLC ("AVP X LLC"), the sole general partner of AVP X GP, (4) ARCH Venture Fund VIII, L.P. ("ARCH Venture Fund VIII"), (5) ARCH Venture Fund VIII Overage, L.P. ("AVF VIII Overage LP"), (6) ARCH Venture Partners VIII, L.P. ("AVP VIII LP") the sole general partner of ARCH Venture Fund VIII, (7) ARCH Venture Partners VIII, LLC ("AVP VIII LLC"), the sole general partner of AVF VIII Overage LP and AVP VIII LP, (7) Keith Crandell ("Crandell"), (8) Robert Nelsen ("Nelsen"), (9) Clinton Bybee ("Bybee", and together with Nelsen and Crandell, collectively the "AVP VIII Managing Directors"), (10) Steven Gillis ("Gillis"), and (11) Kristina Burow ("Burow", and together with Crandell, Nelsen and Gillis, collectively the "AVP X Managing Directors"). Each of the individuals and entities above shall be referred to herein as a "Reporting Person" and collectively as the "Reporting Persons". Each of the AVP VIII Managing Directors and AVP X Managing Directors shall be referred to herein as a "Managing Director" and collectively as "Managing Directors".
  - (b) The business address of each of the Reporting Persons is 8755 West Higgins Road, Suite 1025, Chicago, IL, 60631.
  - (c) The principal business of AVP X GP is to act as the general partner of ARCH X Overage, the principal business of AVP VIII LP is to act as the general partner of ARCH Venture Fund VIII, and the principal business of AVP VIII LLC is to act as the general partner of AVF VIII Overage LP and AVP VIII LP. The principal business of each of the AVP VIII Managing Directors is to act as managing directors of AVP VIII LLC and AVF VIII Overage LP, and the principal business of each of the AVP X Managing Directors is to act as managing directors of AVP X LLC. The AVP VIII Managing Directors, Gillis and Burow act as managing directors of a number of affiliated partnerships with similar businesses.
  - (d) During the five years prior to the date hereof, none of the Reporting Persons has been convicted in a criminal proceeding.
  - (e) During the five years prior to the date hereof, none of the Reporting Persons has been a party to a civil proceeding of a judicial or administrative body of competent jurisdiction ending in a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, Federal or State securities laws or finding any violation with respect to such laws.
  - (f) Each of AVF X Overage, AVP X GP, ARCH Venture Fund VIII, AVF VIII Overage LP and AVP VIII LP are limited partnerships organized under the laws of the State of Delaware. AVP VIII LLC and AVP X LLC are limited liability companies organized under the laws of the State of Delaware. Each Managing Director is a US citizen.
-

**Item 3. Source and Amount of Funds or Other Consideration.**

On February 22, 2019, ARCH Venture Fund VIII closed on the purchase of 150,000 shares of Common Stock at a purchase price of \$2.50 per share. The working capital of ARCH Venture Fund VIII was the source of the funds for the purchase. No part of the purchase price paid by this entity was represented by funds or other consideration borrowed or otherwise obtained for the purpose of acquiring, holding, trading or voting the shares of Common Stock described above. The total amount paid by ARCH Venture Fund VIII for securities purchased in the above-listed transactions is as follows:

ARCH Venture Fund VIII: \$375,000.00

On February 22, 2019, AVF VIII Overage LP closed on the purchase of 150,000 shares of Common Stock at a purchase price of \$2.50 per share. The working capital of AVF VIII Overage LP was the source of the funds for the purchase. No part of the purchase price paid by this entity was represented by funds or other consideration borrowed or otherwise obtained for the purpose of acquiring, holding, trading or voting the shares of Common Stock described above. The total amount paid by AVF VIII Overage LP for securities purchased in the above-listed transactions is as follows:

AVF VIII Overage LP: \$375,000.00

On February 22, 2019, AVF X Overage closed on the purchase of 1,865,800 shares of Common Stock at a purchase price of \$2.50 per share. The working capital of AVF X Overage was the source of the funds for the purchase. No part of the purchase price paid by this entity was represented by funds or other consideration borrowed or otherwise obtained for the purpose of acquiring, holding, trading or voting the shares of Common Stock described above. The total amount paid by AVF X Overage for securities purchased in the above-listed transactions is as follows:

AVF X Overage: \$4,664,500.00

**Item 4. Purpose of Transaction.**

Each of ARCH Venture Fund VIII, AVF VIII Overage LP, and AVF X Overage acquired the Common Stock for investment purposes. Depending on market conditions, the continuing evaluation of the business and prospects of the Issuer and other factors, ARCH Venture Fund VIII, AVF VIII Overage LP, and AVF X Overage and other Reporting Persons may dispose of or acquire additional shares of Common Stock of the Issuer. Except as set forth above, none of the Reporting Persons has any present plans which relate to or would result in:

- (a) The acquisition by any person of additional securities of the Issuer, or the disposition of securities of the Issuer;
  - (b) An extraordinary corporate transaction, such as a merger, reorganization or liquidation, involving the Issuer or any of its subsidiaries;
  - (c) A sale or transfer of a material amount of assets of the Issuer or any of its subsidiaries;
-

- (d) Any change in the present board of directors or management of the Issuer, including any plans or proposals to change the number or term of directors or to fill any existing vacancies on the board;
- (e) Any material change in the present capitalization or dividend policy of the Issuer;
- (f) Any other material change in the Issuer's business or corporate structure;
- (g) Changes in the Issuer's charter, bylaws or instruments corresponding thereto or other actions which may impede the acquisition of control of the Issuer by any person;
- (h) Causing a class of securities of the Issuer to be delisted from a national securities exchange or to cease to be authorized to be quoted in an inter-dealer quotation system of a registered national securities association;
- (i) A class of equity securities of the Issuer becoming eligible for termination of registration pursuant to Section 12(g)(4) of the Securities Exchange Act of 1934; or
- (j) Any action similar to any of those enumerated above.

**Item 5. Interest in Securities of the Issuer.**

- (a) ARCH Venture Fund VIII is the record owner of 2,900,575 shares of Common Stock ("AVF VIII Record Shares"). AVP VIII LP, as the sole general partner of ARCH Venture Fund VIII, may be deemed to beneficially own the AVF VIII Record Shares. AVP VIII LLC, as the sole general partner of AVP VIII LP, may be deemed to beneficially own the AVF VIII Record Shares.

AVF VIII Overage LP is the record holder of 1,032,493 shares of Common Stock ("VIII Overage Record Shares"). AVP VIII LLC, as the sole general partner of AVF VIII Overage LP, may be deemed to beneficially own the VIII Overage Record Shares.

AVF X Overage is the record holder of 1,865,800 shares of Common Stock ("X Overage Record Shares"). AVP X Overage LP, as the sole general partner of AVF X Overage, may be deemed to beneficially own the X Overage Record Shares. AVF X LLC, as the sole general partner of AVP X Overage LP, may be deemed to beneficially own the X Overage Record Shares.

By virtue of their relationship as affiliated entities who have overlapping general partners and managing directors, each entity and Reporting Person may be deemed to share the power to direct the disposition and vote of the AVF VIII Record Shares, VIII Overage Record Shares, and X Overage Record Shares (collectively, the "Record Shares"). In addition, each of the AVP VIII Managing Directors may be deemed to share the power to direct the disposition and vote of the AVF VIII Record Shares and VIII Overage Record Shares, and each of the AVP X Managing Directors may be deemed to share the power to direct the disposition and vote of the X Overage Record Shares. Each Reporting Person disclaims beneficial ownership of all securities except for the shares, if any, held of record by such Reporting Person.

---

The percentage of outstanding Common Stock of the Issuer which may be deemed to be beneficially owned by each Reporting Person is set forth on Line 13 of such Reporting Person's cover sheet. Such percentage was calculated based on the 29,140,101 shares of Common Stock reported by the Issuer to be outstanding after the closing of the Issuer's follow on public offering on February 22, 2019 in the Issuer's prospectus Form 424B5 filed with the Securities and Exchange Commission on February 21, 2019.

- (b) Regarding the number of shares as to which such person has:
  - (i) sole power to vote or to direct the vote: See line 7 of cover sheets.
  - (ii) shared power to vote or to direct the vote: See line 8 of cover sheets.
  - (iii) sole power to dispose or to direct the disposition: See line 9 of cover sheets.
  - (iv) shared power to dispose or to direct the disposition: See line 10 of cover sheets.
- (c) Except as set forth above, none of the Reporting Persons has effected any transaction in the Common Stock during the last 60 days.
- (e) No other person is known to have the right to receive or the power to direct the receipt of dividends from, or any proceeds from the sale of, shares beneficially owned by any of the Reporting Persons.
- (f) Not applicable

**Item 6. Contracts, Arrangements, Undertakings or Relationships with Respect to Securities of the Issuer.**

ARCH Venture Fund VIII and AVF VIII Overage Fund, L.P. are parties to that certain Amended and Restated Investors' Rights Agreement, dated April 12, 2017 (the "Investor Rights Agreement"), which is attached as an exhibit to the Issuer's Form S-1 filed on July 3, 2017 and incorporated by reference herein. Effective as of the closing of the Issuer's initial public offering, the covenants relating to inspection and information rights set forth in Section 3 were terminated. Pursuant to the Investor Rights Agreement, ARCH Venture Fund VIII and AVF VIII Overage, L.P. I have certain registration rights with respect to its Common Stock. ARCH Venture Fund VIII, AVF VIII Overage Fund, L.P., AVF X Overage and Burow have entered into lock-up agreements with the underwriters of the Issuer's follow on public offering on February 22, 2019 pursuant to which ARCH Venture Fund VIII, AVF VIII Overage Fund, L.P., AVF X Overage and Burow have generally agreed, subject to certain exceptions, not to offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the Common Stock for a period of 60 days after February 22, 2019.

**Item 7. Material to be Filed as Exhibits.**

Exhibit 1- Agreement of Joint Filing

---

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: March 6, 2019

ARCH VENTURE FUND VIII, L.P.

By: ARCH Venture Partners VIII, L.P.  
its General Partner

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS VIII, L.P.

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS VIII, LLC

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE FUND VIII OVERAGE, L.P.

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE FUND X OVERAGE, L.P.

By: ARCH Venture Partners X Overage, L.P.  
its General Partner

By: ARCH Venture Partners X, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

---

ARCH VENTURE PARTNERS X OVERAGE, L.P.

By: ARCH Venture Partners X, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS X, LLC

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

\_\_\_\_\_  
\*  
Keith Crandell

\_\_\_\_\_  
\*  
Clinton Bybee

\_\_\_\_\_  
\*  
Robert Nelsen

\_\_\_\_\_  
\*  
Steven Gillis

\_\_\_\_\_  
\*  
Kristina Burow

\* By: /s/ Mark McDonnell  
Mark McDonnell  
Attorney-in-Fact

\* This Schedule 13D was executed by Mark McDonnell pursuant to a Power of Attorney filed as Exhibit 24 to the Form 4 relating to the beneficial ownership of shares of Sienna Biopharmaceuticals, Inc. by the Reporting Persons filed with the Securities Exchange Commission on February 26, 2019 and incorporated herein in its entirety by reference.

EXHIBIT 1AGREEMENT OF JOINT FILING

Pursuant to Rule 13d-1(k)(1) under the Securities Exchange Act of 1934, the undersigned hereby agree that only one statement containing the information required by Schedule 13D need be filed with respect to the ownership by each of the undersigned of shares of Common Stock of Sienna Biopharmaceuticals, Inc.

This Agreement may be executed in any number of counterparts, each of which shall be deemed an original.

Date: March 6, 2019

ARCH VENTURE FUND VIII, L.P.

By: ARCH Venture Partners VIII, L.P.  
its General Partner

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS VIII, L.P.

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS VIII, LLC

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE FUND VIII OVERAGE, L.P.

By: ARCH Venture Partners VIII, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE FUND X OVERAGE, L.P.

By: ARCH Venture Partners X Overage, L.P.  
its General Partner

By: ARCH Venture Partners X, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

---

ARCH VENTURE PARTNERS X OVERAGE, L.P.

By: ARCH Venture Partners X, LLC  
its General Partner

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

ARCH VENTURE PARTNERS X, LLC

By: \_\_\_\_\_  
\*  
Keith Crandell  
Managing Director

\_\_\_\_\_  
\*  
Keith Crandell

\_\_\_\_\_  
\*  
Clinton Bybee

\_\_\_\_\_  
\*  
Robert Nelsen

\_\_\_\_\_  
\*  
Steven Gillis

\_\_\_\_\_  
\*  
Kristina Burow

\* By: /s/ Mark McDonnell  
Mark McDonnell as  
Attorney-in-Fact

\* This Agreement of Joint Filing was executed by Mark McDonnell pursuant to a Power of Attorney filed as Exhibit 24 to the Form 4 relating to the beneficial ownership of shares of Sienna Biopharmaceuticals, Inc. by the Reporting Persons filed with the Securities Exchange Commission on February 26, 2019 and incorporated herein in its entirety by reference.