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

**SCHEDULE 13D**  
Under the Securities Exchange Act of 1934  
(Amendment No. 2)

**PIERIS PHARMACEUTICALS, INC.**

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(Name of Issuer)

**COMMON STOCK**

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(Title of Class of Securities)

**720795103**

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(CUSIP Number)

**OrbiMed Advisors LLC  
OrbiMed Capital GP III LLC  
Samuel D. Isaly**

**601 Lexington Avenue, 54th Floor  
New York, NY 10022  
Telephone: (212) 739-6400**

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

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

**January 3, 2018**

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(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(b) 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).

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CUSIP No. 720795103

|  |   |  |
|--|---|--|
| 1  | NAME OF REPORTING PERSONS<br>OrbiMed Advisors LLC   |  |
| 2  | CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP<br>(a) <input checked="" type="checkbox"/><br>(b) <input type="checkbox"/> |  |
| 3  | SEC USE ONLY  |  |
| 4  | SOURCE OF FUNDS<br>AF   |  |
| 5  | CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>            |  |
| 6  | CITIZENSHIP OR PLACE OF ORGANIZATION<br>Delaware  |  |
| NUMBER OF<br>SHARES<br>BENEFICIALLY<br>OWNED BY<br>EACH<br>REPORTING<br>PERSON<br>WITH | 7   | SOLE VOTING POWER<br>0                 |
|  | 8   | SHARED VOTING POWER<br>5,550,000*      |
|  | 9   | SOLE DISPOSITIVE POWER<br>0            |
|  | 10  | SHARED DISPOSITIVE POWER<br>5,550,000* |
| 11   | AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON<br>5,550,000*  |  |
| 12   | CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>           |  |
| 13   | PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)<br>12.39%*   |  |
| 14   | TYPE OF REPORTING PERSON (See Instructions)<br>IA   |  |

\* This percentage is calculated based upon 44,794,308 shares of common stock, par value \$0.001 per share (the "Shares"), outstanding of Pieris Pharmaceuticals, Inc., a Nevada corporation (the "Issuer"), as set forth in the Issuer's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 13, 2017.

|   |  |
|---|--|
| CUSIP No. 720795103   |  |
| 1   | NAME OF REPORTING PERSONS<br>OrbiMed Capital GP III LLC  |
| 2   | CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (a) <input checked="" type="checkbox"/><br>(b) <input type="checkbox"/> |
| 3   | SEC USE ONLY   |
| 4   | SOURCE OF FUNDS<br>AF  |
| 5   | CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>         |
| 6   | CITIZENSHIP OR PLACE OF ORGANIZATION<br>Delaware   |
| NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH | 7 SOLE VOTING POWER<br>0   |
|   | 8 SHARED VOTING POWER<br>5,500,730*  |
|   | 9 SOLE DISPOSITIVE POWER<br>0  |
|   | 10 SHARED DISPOSITIVE POWER<br>5,500,730*  |
| 11  | AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON<br>5,500,730*   |
| 12  | CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>        |
| 13  | PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)<br>12.28%*  |
| 14  | TYPE OF REPORTING PERSON (See Instructions)<br>OO  |

\* This percentage is calculated based upon 44,794,308 shares of common stock, par value \$0.001 per share (the "Shares"), outstanding of Pieris Pharmaceuticals, Inc., a Nevada corporation (the "Issuer"), as set forth in the Issuer's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 13, 2017.

|   |   |
|---|---|
| CUSIP No. 720795103   |   |
| 1   | NAME OF REPORTING PERSONS<br>Samuel D. Isaly  |
| 2   | CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP<br>(a) <input checked="" type="checkbox"/><br>(b) <input type="checkbox"/> |
| 3   | SEC USE ONLY  |
| 4   | SOURCE OF FUNDS<br>AF   |
| 5   | CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>            |
| 6   | CITIZENSHIP OR PLACE OF ORGANIZATION<br>Delaware  |
| NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH | 7<br>SOLE VOTING POWER<br>0   |
|   | 8<br>SHARED VOTING POWER<br>5,550,000*  |
|   | 9<br>SOLE DISPOSITIVE POWER<br>0  |
|   | 10<br>SHARED DISPOSITIVE POWER<br>5,550,000*  |
| 11  | AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON<br>5,550,000*  |
| 12  | CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>           |
| 13  | PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)<br>12.39%*   |
| 14  | TYPE OF REPORTING PERSON (See Instructions)<br>IN   |

\* This percentage is calculated based upon 44,794,308 shares of common stock, par value \$0.001 per share (the "Shares"), outstanding of Pieris Pharmaceuticals, Inc., a Nevada corporation (the "Issuer"), as set forth in the Issuer's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on November 13, 2017.

### Item 1. Security and Issuer

This Amendment No. 2 ("Amendment No. 2") to Schedule 13D supplements and amends the Statement on Schedule 13D of OrbiMed Advisors LLC, OrbiMed Capital GP III LLC and Samuel D. Isaly originally filed with the Securities and Exchange Commission (the "SEC") on July 9, 2015 (the "Statement") and amended by Amendment No. 1 thereto filed with the SEC on July 12, 2016. The Statement relates to the common stock, par value \$0.001 per share (the "Shares"), of Pieris Pharmaceuticals, Inc., a corporation organized under the laws of Nevada (the "Issuer"), with its principal executive offices located at 255 State Street, 9th Floor, Boston, MA 02109. The Shares are listed on the NASDAQ Global Market under the ticker symbol "PIRS". Information given in response to each item shall be deemed incorporated by reference in all other items, as applicable.

### Item 2. Identity and Background

(a) This Amendment No. 2 to the Statement is being filed by OrbiMed Advisors LLC ("Advisors"), a limited liability company organized under the laws of Delaware, OrbiMed Capital GP III LLC ("GP III"), a limited liability company organized under the laws of Delaware, and Samuel D. Isaly ("Isaly"), an individual (collectively, the "Reporting Persons").

(b) – (c) Advisors, a registered investment adviser under the Investment Advisers Act of 1940, as amended, is the sole general partner of OrbiMed Associates III, LP ("Associates III") and the sole managing member of GP III, which is the sole general partner of OrbiMed Private Investments III, LP ("OPI III"). OPI III and Associates III hold Shares as described herein. Advisors, GP III, and Isaly have their principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

The directors and executive officers of Advisors and GP III are set forth on Schedules I and II, attached hereto. Schedules I and II set forth the following information with respect to each such person:

- (i) name;
- (ii) business address;
- (iii) present principal occupation or employment and the name, principal business and address of any corporation or other organization in which such employment is conducted;
- (iv) citizenship.

(d) – (e) During the last five years, neither the Reporting Persons nor any Person named in Schedule I or II have been (i) convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors) or (ii) a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding was or is subject to 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) Isaly is a citizen of the United States.

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

Not applicable.

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#### **Item 4. Purpose of Transaction**

This Amendment No. 2 to the Statement relates to the transactions by the Reporting Persons more fully described in Item 5 below. The Shares initially had been acquired by the Reporting Persons for the purpose of making an investment in the Issuer and not with the intention of acquiring control of the Issuer's business.

The Reporting Persons from time to time intend to review their investment in the Issuer on the basis of various factors, including the Issuer's business, financial condition, results of operations and prospects, general economic and industry conditions, the securities markets in general and those for the Issuer's common stock in particular, as well as other developments and other investment opportunities. Based upon such review, the Reporting Persons will take such actions in the future as the Reporting Persons may deem appropriate in light of the circumstances existing from time to time. If the Reporting Persons believe that further investment in the Issuer is attractive, whether because of the market price of the common stock or otherwise, they may acquire Shares or other securities of the Issuer either in the open market or in privately negotiated transactions. Similarly, depending on market and other factors, the Reporting Persons may determine to dispose of some or all of the Shares currently owned by the Reporting Persons or otherwise acquired by the Reporting Persons either in the open market or in privately negotiated transactions.

Except as set forth in this Statement, the Reporting Persons have not formulated any plans or proposals 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 the 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 Issuer's capitalization or dividend policy of the Issuer, (f) any other material change in the Issuer's business or corporate structure, (g) any change in the Issuer's charter or bylaws or other instrument corresponding thereto or other action which may impede the acquisition of control of the Issuer by any person, (h) causing a class of the Issuer's securities to be deregistered or 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 Act or (j) any action similar to any of those enumerated above.

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

(a) – (b) As of the date of this filing, Advisors, GP III and Isaly may be deemed, for purposes of Rule 13d-3 of the Act, directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares. Based upon information contained in the Issuer's Quarterly Report on Form 10-Q filed with the SEC on November 13, 2017, such Shares deemed to be indirectly beneficially owned by GP III constitutes approximately 12.28% of the issued and outstanding Shares, and such Shares deemed to be indirectly beneficially owned by Advisors and Isaly constitutes approximately 12.39% of the issued and outstanding Shares. Advisors, pursuant to its authority as the sole managing member of GP III, which is the sole general partner of OPI III, and as the sole general partner of Associates III, may be deemed to indirectly beneficially own the Shares held by OPI III and Associates III. GP III, pursuant to its authority as the general partner of OPI III, may be deemed to indirectly beneficially own the Shares held by OPI III. Isaly, pursuant to his authority as the managing member of Advisors and owner of a controlling interest in Advisors, pursuant to its limited liability company agreement, may be deemed to also indirectly beneficially own the Shares attributable to Advisors. As a result, Isaly, Advisors and GP III share the power to direct the vote and the disposition of the Shares held by OPI III described in Item 6 below, and Isaly and Advisors share the power to direct the vote and the disposition of the Shares held by Associates III.

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In addition, Advisors and GP III, pursuant to their authority under the limited partnership agreements of OPI III and/or Associates III, prior to the date of this filing, caused OPI III and Associates III, as applicable, to enter into the agreements referred to in Item 6 below.

(c)

| <b>Seller</b>  | <b>Date of Transaction</b> | <b>Transaction</b>                          | <b>Number of Shares</b> | <b>Price Per Share*</b> |
|----------------|----------------------------|---|-------------------------|-------------------------|
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 27,241                  | \$2.00                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 259                     | \$2.00                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 5,227                   | \$3.00                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 50                      | \$3.00                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 6,654                   | \$2.62                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 63                      | \$2.62                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 8,717                   | \$1.94                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 83                      | \$1.94                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 10,180                  | \$1.62                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 97                      | \$1.62                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 19,811                  | \$1.59                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 189                     | \$1.59                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 8,097                   | \$2.05                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 77                      | \$2.05                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 9,642                   | \$1.73                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 92                      | \$1.73                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 10,182                  | \$1.64                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 97                      | \$1.64                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 14,858                  | \$2.01                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 142                     | \$2.01                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 10,216                  | \$2.01                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 97                      | \$2.01                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 10,447                  | \$2.32                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 99                      | \$2.32                  |
| OPI III        | December 18, 2017          | Acquired upon the exercise of stock options | 4,971                   | \$5.64                  |
| Associates III | December 18, 2017          | Acquired upon the exercise of stock options | 47                      | \$5.64                  |
| OPI III        | December 18, 2017          | Sold  | 146,243                 | \$5.70                  |
| Associates III | December 18, 2017          | Sold  | 1,392                   | \$5.70                  |
| OPI III        | January 3, 2018            | Sold  | 1,693,492               | \$7.35                  |
| Associates III | January 3, 2018            | Sold  | 16,128                  | \$7.35                  |

\* The Shares were sold in a block order at a price of \$5.70 (December 18, 2017) and \$7.35 (January 3, 2018).

Except as disclosed above, the Reporting Persons have not effected any transactions in the shares during the past sixty (60) days.

(d) Not applicable.

(e) Not applicable.

**Item 6. Contracts, Arrangements, Understandings or Relationship with Respect to Securities of the Issuer**

In addition to the relationships between the Reporting Persons described in Items 2, 3 and 5 above, GP III is the sole general partner of OPI III, pursuant to the terms of the limited partnership agreement of OPI III. Advisors is the sole managing member of GP III, pursuant to the terms of the limited liability company agreement of GP III, and the sole general partner of Associates III, pursuant to the terms of the limited partnership agreement of Associates III. Pursuant to these agreements and relationships, Advisors and GP III have discretionary investment management authority with respect to the assets of OPI III, and Advisors has discretionary investment management authority with respect to the assets of Associates III. Such authority includes the power of GP III and Advisors to vote and otherwise dispose of securities purchased by OPI III, and the power of Advisors to vote and otherwise dispose of securities purchased by Associates III. The number of outstanding Shares held of record by OPI III is 5,500,730, and the number of outstanding Shares held of record by Associates III is 49,270. Advisors may be considered to hold indirectly 5,550,000 Shares, and GP III may be considered to hold indirectly 5,500,730 Shares.

Chau Khuong (“Khuong”), an employee of Advisors, was a member of the Board of Directors of the Issuer from July 2014 to November 2017, and accordingly, the Reporting Persons may have had the ability to affect and influence control of the Issuer during this time. From time to time, Khuong received stock options pursuant to the Issuer’s compensation arrangements for non-employee directors. Khuong was obligated to transfer any Shares issued under any such stock options or other awards to the Reporting Persons, which in turn ensured that such shares or economic benefits were provided to OPI III and Associates on a pro-rata basis. Khuong stepped down from the Board of Directors of the Issuer on November 11, 2017.

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**Item 7. Materials to Be Filed as Exhibits**

Exhibit 1 - Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital GP III LLC and Samuel D. Isaly.

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**SIGNATURE**

After reasonable inquiry and to the best of each of the undersigned's knowledge and belief, each of the undersigned certifies that the information set forth in this statement is true, complete and correct.

Dated: January 5, 2018

OrbiMed Advisors LLC

By: /s/ Samuel D. Isaly  
Name: Samuel D. Isaly  
Title: Managing Member

OrbiMed Capital GP III LLC

By: OrbiMed Advisors LLC  
its Managing Member

By: /s/ Samuel D. Isaly  
Name: Samuel D. Isaly  
Title: Managing Member

Samuel D. Isaly

/s/ Samuel D. Isaly  
Name: Samuel D. Isaly

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**Schedule I**

The name and present principal occupation of each of the executive officers and directors of OrbiMed Advisors LLC are set forth below. Unless otherwise noted, each of these persons are United States citizens and have as their business address 601 Lexington Avenue, 54th Floor, New York, NY 10022.

| Name  | Position with Reporting Person | Principal Occupation                            |
|---|--------------------------------|---|
| Samuel D. Isaly                             | Managing Member                | Managing Member<br>OrbiMed Advisors LLC         |
| Carl L. Gordon                              | Member                         | Member<br>OrbiMed Advisors LLC                  |
| Sven H. Borho<br>German and Swedish Citizen | Member                         | Member<br>OrbiMed Advisors LLC                  |
| Jonathan T. Silverstein                     | Member                         | Member<br>OrbiMed Advisors LLC                  |
| W. Carter Neild                             | Member                         | Member<br>OrbiMed Advisors LLC                  |
| Geoffrey C. Hsu                             | Member                         | Member<br>OrbiMed Advisors LLC                  |
| Evan D. Sotiriou                            | Chief Financial Officer        | Chief Financial Officer<br>OrbiMed Advisors LLC |

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## Schedule II

The business and operations of OrbiMed Capital GP III LLC are managed by the executive officers and directors of its managing member, OrbiMed Advisors LLC, set forth on Schedule I.

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JOINT FILING AGREEMENT

The undersigned hereby agree that the Statement on this Schedule 13D, dated January 5, 2018 (the "Schedule 13D"), with respect to the Common Stock, of Pieris Pharmaceuticals, Inc. is filed on behalf of each of us pursuant to and in accordance with the provisions of Rule 13d-1(k) under the Securities Exchange Act of 1934, as amended, and that this Agreement shall be included as an Exhibit to this Schedule 13D. Each of the undersigned agrees to be responsible for the timely filing of the Schedule 13D, and for the completeness and accuracy of the information concerning itself contained therein. This Agreement may be executed in any number of counterparts, all of which taken together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the undersigned have executed this Agreement as of the 5<sup>th</sup> day of January 2018.

OrbiMed Advisors LLC

By: /s/ Samuel D. Isaly  
Name: Samuel D. Isaly  
Title: Managing Member

OrbiMed Capital GP III LLC

By: OrbiMed Advisors LLC  
its Managing Member

By: /s/ Samuel D. Isaly  
Name: Samuel D. Isaly  
Title: Managing Member

Samuel D. Isaly

/s/ Samuel D. Isaly  
Name: Samuel D. Isaly

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