

(Print or Type Responses)

|   |   |  |                                   |  |  |   |  |                     |
|---|---|--|-----------------------------------|--|--|---|--|---------------------|
| 1. Name and Address of Reporting Person *<br>FROST PHILLIP MD ET AL |   | 2. Issuer Name and Ticker or Trading Symbol<br>OPKO HEALTH, INC. [OPK]           |                                   | 5. Relationship of Reporting Person(s) to Issuer<br>(Check all applicable)<br><input type="checkbox"/> Director <input checked="" type="checkbox"/> 10% Owner<br><input checked="" type="checkbox"/> Officer (give title below) <input type="checkbox"/> Other (specify below)<br>CEO & Chairman |  |   |  |                     |
| (Last) (First) (Middle)<br>OPKO HEALTH, INC., 4400 BISCAYNE BLVD.   |   | 3. Date of Earliest Transaction (Month/Day/Year)<br>02/25/2022                   |                                   |  |  |   |  |                     |
| (Street)<br>MIAMI, FL 33137   |   | 4. If Amendment, Date Original Filed(Month/Day/Year)                             |                                   | 6. Individual or Joint/Group Filing (Check Applicable Line)<br><input type="checkbox"/> Form filed by One Reporting Person<br><input checked="" type="checkbox"/> Form filed by More than One Reporting Person   |  |   |  |                     |
| (City) (State) (Zip)  |   | Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned |                                   |  |  |   |  |                     |
| 1. Title of Security<br>(Instr. 3)                                  | 2. Transaction Date<br>(Month/Day/Year) | 2A. Deemed Execution Date, if any<br>(Month/Day/Year)                            | 3. Transaction Code<br>(Instr. 8) | 4. Securities Acquired (A) or Disposed of (D)<br>(Instr. 3, 4 and 5)   | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s)<br>(Instr. 3 and 4) | 6. Ownership Form: Direct (D) or Indirect (I)<br>(Instr. 4) | 7. Nature of Indirect Beneficial Ownership<br>(Instr. 4) |                     |
| Common Stock  |   |  |                                   |  | 3,068,951  | D   |  |                     |
| Common Stock  | 02/25/2022                              |  | P                                 | 750,000 A  | \$ 3.0871<br>(1)   | 194,521,694   | I  | See Footnote<br>(2) |
| Common Stock  |   |  |                                   |  | 30,127,177   | I   | See Footnote<br>(3)                                      |                     |

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

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.

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| Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned<br>(e.g., puts, calls, warrants, options, convertible securities) |  |   |   |                                   |   |  |     |   |                 |  |                            |   |   |   |   |
|---|--|---|---|-----------------------------------|---|--|-----|---|-----------------|--|----------------------------|---|---|---|---|
| 1. Title of Derivative Security<br>(Instr. 3)   | 2. Conversion or Exercise Price of Derivative Security | 3. Transaction Date<br>(Month/Day/Year) | 3A. Deemed Execution Date, if any<br>(Month/Day/Year) | 4. Transaction Code<br>(Instr. 8) |   | 5. Number of Derivative Securities Acquired (A) or Disposed of (D)<br>(Instr. 3, 4, and 5) |     | 6. Date Exercisable and Expiration Date<br>(Month/Day/Year) |                 | 7. Title and Amount of Underlying Securities<br>(Instr. 3 and 4) |                            | 8. Price of Derivative Security<br>(Instr. 5) | 9. Number of Derivative Securities Beneficially Owned Following Reported Transaction(s)<br>(Instr. 4) | 10. Ownership Form of Derivative Security: Direct (D) or Indirect (I)<br>(Instr. 4) | 11. Nature of Indirect Beneficial Ownership<br>(Instr. 4) |
|   |  |   |   | Code                              | V | (A)  | (D) | Date Exercisable  | Expiration Date | Title  | Amount or Number of Shares |   |   |   |   |

Reporting Owners

| Reporting Owner Name / Address  | Relationships |           |                |       |
|---|---------------|-----------|----------------|-------|
|   | Director      | 10% Owner | Officer        | Other |
| FROST PHILLIP MD ET AL<br>OPKO HEALTH, INC.<br>4400 BISCAYNE BLVD.<br>MIAMI, FL 33137 | X             | X         | CEO & Chairman |       |
| Frost Gamma Investments Trust<br>4400 BISCAYNE BLVD.<br>MIAMI, FL 33137               |               | X         |                |       |

# Signatures

|  |  |                     |
|--|--|---------------------|
| Phillip Frost, M.D., Individually and as Trustee |  | 02/28/2022          |
| <small>**Signature of Reporting Person</small>   |  | <small>Date</small> |

## Explanation of Responses:

\* If the form is filed by more than one reporting person, *see* Instruction 4(b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations. *See* 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

(1) The price reported is a weighted average price. These shares were purchased in multiple transactions at prices ranging from \$2.81 to \$3.20, inclusive. The reporting person undertakes to provide to OPKO Health, Inc. (the "Company"), any security holder of the Company or the staff of the Securities and Exchange Commission, upon request, full information regarding the number of shares purchased at each separate price within the range set forth in footnote (1) to this Form 4.

(2) The securities are held by Frost Gamma Investments Trust, of which Phillip Frost M.D., is the trustee. Frost Gamma L.P. is the sole and exclusive beneficiary of Frost Gamma Investments Trust. Dr. Frost is one of two limited partners of Frost Gamma L.P. The general partner of Frost Gamma L.P. is Frost Gamma, Inc., and the sole shareholder of Frost Gamma, Inc. is Frost-Nevada Corporation. Dr. Frost is also the sole shareholder of Frost-Nevada Corporation. The reporting person disclaims beneficial ownership of these securities, except to the extent of any pecuniary interest therein and this report shall not be deemed an admission that the reporting person is the beneficial owner of these securities for purposes of Section 16 or for any other purpose.

(3) These securities are held by Frost Nevada Investments Trust, of which the Reporting Person is the trustee and Frost-Nevada, L.P. is the sole and exclusive beneficiary. The Reporting Person is one of seven limited partners of Frost-Nevada, L.P. and the sole shareholder of Frost-Nevada Corporation, the sole general partner of Frost-Nevada, L.P. The reporting person disclaims beneficial ownership of these securities, except to the extent of any pecuniary interest therein and this report shall not be deemed an admission that the reporting person is the beneficial owner of these securities for purposes of Section 16 or for any other purpose.

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, *see* Instruction 6 for procedure.

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

JOINT FILER INFORMATION

Name: Frost Gamma Investments Trust

Address:  
4400 Biscayne Blvd.  
Miami, FL 33137

Designated Filer: Phillip Frost, M.D.

Issuer Name and Ticker Symbol: OPKO Health, Inc. (OPK)

Date of Earliest Transaction: February 25, 2022

Relationship to Issuer: 10% Owner

FROST GAMMA INVESTMENTS TRUST

By: /s/ Phillip Frost, M.D., as Trustee  
Phillip Frost, M.D., Trustee