

**INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES**

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

| OMB APPROVAL                                 |           |
|----------------------------------------------|-----------|
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|                                                                                                                                                                                                                                                                          |                                                                                   |                                                                                                                                                                                              |                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Name and Address of Reporting Person*</b><br><u>KLEIN JOSEPH III</u><br>_____<br>(Last) (First) (Middle)<br><u>C/O ISIS PHARMACEUTICALS, INC.</u><br><u>1896 RUTHERFORD ROAD</u><br>_____<br>(Street)<br><u>CARLSBAD CA 92008</u><br>_____<br>(City) (State) (Zip) | <b>2. Date of Event Requiring Statement (Month/Day/Year)</b><br><u>12/13/2005</u> | <b>3. Issuer Name and Ticker or Trading Symbol</b><br><u>ISIS PHARMACEUTICALS INC [ ISIS ]</u>                                                                                               | <b>5. If Amendment, Date of Original Filed (Month/Day/Year)</b>                                                                                                                              |
|                                                                                                                                                                                                                                                                          |                                                                                   | <b>4. Relationship of Reporting Person(s) to Issuer (Check all applicable)</b><br><input checked="" type="checkbox"/> Director 10% Owner<br>Officer (give title below) Other (specify below) | <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b><br><input checked="" type="checkbox"/> Form filed by One Reporting Person<br>Form filed by More than One Reporting Person |

**Table I - Non-Derivative Securities Beneficially Owned**

| 1. Title of Security (Instr. 4) | 2. Amount of Securities Beneficially Owned (Instr. 4) | 3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5) | 4. Nature of Indirect Beneficial Ownership (Instr. 5) |
|---------------------------------|-------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------|
| Common Stock                    | 100                                                   | I                                                        | Owned by Son                                          |

**Table II - Derivative Securities Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

| 1. Title of Derivative Security (Instr. 4) | 2. Date Exercisable and Expiration Date (Month/Day/Year) |                 | 3. Title and Amount of Securities Underlying Derivative Security (Instr. 4) | 4. Conversion or Exercise Price of Derivative Security | 5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5) | 6. Nature of Indirect Beneficial Ownership (Instr. 5) |
|--------------------------------------------|----------------------------------------------------------|-----------------|-----------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------|
|                                            | Date Exercisable                                         | Expiration Date |                                                                             |                                                        |                                                          |                                                       |

Explanation of Responses:

Remarks:

/s/B. Lynne Parshall, Attorney-in-Fact

12/15/2005

\*\* Signature of Reporting Person

Date

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

\* If the form is filed by more than one reporting person, see Instruction 5 (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).

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

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 Number.

POWER OF ATTORNEY

Know all by these presents, that the undersigned hereby constitutes and appoints each of Stanley T. Crooke and B. Lynne Parshall, signing individually, the undersigned (1) execute for and on behalf of the undersigned, an officer, director or holder of 10% or more of a registered class of securities of Isis Pharmaceuticals, Inc. (Isis), (2) do and perform any and all acts for and on behalf of the undersigned that may be necessary or desirable to complete and execute such Form 3, 4 or 5, complete and file such Form 3, 4 or 5, (3) take any other action of any nature whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit, in the best interest of Isis. The undersigned hereby grants to each such attorney-in-fact full power and authority to do and perform any and every act and thing whatsoever requisite, necessary, convenient or proper in the premises, and which the undersigned might lawfully do or perform in person. This Power of Attorney shall remain in full force and effect until the earliest to occur of (a) the undersigned is no longer required to file Forms 3, 4 and 5 with the SEC.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed as of this 13th day of December, 2005.

/S/JOSEPH KLEIN III