

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

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

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

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/15/2005	12/15/2005	p ⁽¹⁾		2,000 ⁽¹⁾	A	\$5.18	2,000	D	
Common Stock								100	I	By Son

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)	
				Code	V	(A)	(D)	Date Exercisable	Expiration Date						Title
Director Stock Option (right to buy)	\$5.17	12/13/2005	12/13/2005	A		20,000		12/13/2009 ⁽²⁾	12/12/2015	Common Stock	20,000	\$0	20,000	D	

Explanation of Responses:

- The purchase reported in this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 12-13-05.
- Grant of 12-13-05 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, with the first installment vesting on 12-13-06. The option shall be fully vested and exercisable on 12-13-09. The option is exercisable as to 0 shares on 12-13-05.

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 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).

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.