

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

OMB APPROVAL	
OMB Number:	3235-0287
Estimated average burden hours per response:	0.5

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>BENNETT C FRANK</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>	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Senior Vice President</u>
	3. Date of Earliest Transaction (Month/Day/Year) <u>04/01/2008</u>	
	4. If Amendment, Date of Original Filed (Month/Day/Year)	

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	04/01/2008	04/01/2008	M ⁽¹⁾		10,000 ⁽¹⁾	A	\$5.25	10,392	D	
Common Stock	04/01/2008	04/01/2008	S ⁽²⁾		10,000 ⁽²⁾	D	\$15.33	392	D	

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
Employee Stock Purchase (right to buy)	\$5.25	04/01/2008	04/01/2008	M			10,000	01/03/2007 ⁽³⁾	01/02/2013	Common Stock	10,000	\$0	20,322	D	

Explanation of Responses:

- The purchase reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 3/12/08.
- The sale reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 3/12/08.
- Grant of 1-3-06 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1-3-07. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 7,581 shares per year. The option was exercisable as to 16,425 shares on 4-1-08.

Remarks:

/s/C. Frank Bennett 04/03/2008
 ** 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.