

**PROSPECTUS SUPPLEMENT  
(TO PROSPECTUS DATED May 30, 2006)**

**3,383,651 Shares**

**ISIS PHARMACEUTICALS, INC.**

**Common Stock**

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You should read this prospectus supplement and the accompanying prospectus carefully before you invest. Both documents contain information you should consider carefully before making your investment decision.

Pursuant to this prospectus supplement and the accompanying prospectus, we are directly offering 3,383,651 shares of our common stock to Symphony GenIsis Holdings LLC, or Symphony Holdings, pursuant to our purchase option agreement, dated April 7, 2006, with Symphony Holdings.

We are issuing the shares in partial consideration for the purchase by Isis of all of the equity of Symphony GenIsis, Inc. Symphony GenIsis is the entity formed in April 2006 by Symphony Holdings, and capitalized with \$75 million, to fund development of three of our drugs. As part of the transaction, we licensed to Symphony GenIsis our apoB-targeted antisense drug, ISIS 301012, as well as two preclinical antisense drugs, ISIS 325568 and ISIS 377131, targeting glucagon receptor and glucocorticoid receptor to treat diabetes.

The purchase option agreement allows us to reacquire the licensed programs at any time by acquiring all of Symphony GenIsis' equity for \$120,000,000 with a combination of cash and our common stock (for up to 33% of the purchase price). We are paying \$39,600,000 of this price in shares of our common stock and the remainder in cash. As a result, we are issuing 3,383,651 shares of our common stock to Symphony Holdings. Pursuant to the purchase option agreement, the shares of our common stock were valued at \$11.70 per share, based on the average closing price of our common stock on the Nasdaq Global Market for the 60 trading days preceding September 21, 2007.

Our common stock is quoted on the Nasdaq National Market under the symbol "ISIS."

We expect to issue the shares to Symphony Holdings on or about September 27, 2007.

On September 26, 2007, the last reported sales price for our common stock was \$15.10 per share.

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**Investing in our common stock involves risks.**

**See "Risk Factors" beginning on page 3 of the accompanying prospectus as amended or updated in subsequent filings with the securities and exchange commission and incorporated by reference in this prospectus supplement and the accompanying prospectus.**

You should rely only on the information provided or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement and the accompanying prospectus is accurate as of any date other than the date on the front of these documents.

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**Neither the securities and exchange commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

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The date of this Prospectus Supplement is September 26, 2007

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