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**United States**  
**SECURITIES AND EXCHANGE COMMISSION**  
WASHINGTON, D.C. 20549

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**SCHEDULE 13G**

Under the Securities Exchange Act of 1934  
(Amendment No. 4)\*

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**ISIS PHARMACEUTICALS, INC.**

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(Name of Issuer)

**Common Stock**

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(Title of Class of Securities)

**464330109**

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(CUSIP Number)

**December 31, 2014**

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(Date of Event Which Requires Filing This Statement)

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Check the appropriate box to designate the rule pursuant to which this Schedule is filed:

Rule 13d-1(b)

Rule 13d-1(c)

Rule 13d-1(d)

\* The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter the disclosures provided in a prior cover page.

The information required in the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

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1.	Names of Reporting Persons <b>BB Biotech AG</b>	
2.	Check the Appropriate Box if a Member of a Group (See Instructions) (a) <input checked="" type="checkbox"/> (b) <input type="checkbox"/>	
3.	SEC Use Only	
4.	Citizenship or Place of Organization <b>Switzerland</b>	
Number of Shares Beneficially Owned by Each Reporting Person with:	5.	Sole Voting Power <b>0</b>
	6.	Shared Voting Power <b>5,976,526</b>
	7.	Sole Dispositive Power <b>0</b>
	8.	Shared Dispositive Power <b>5,976,526</b>
9.	Aggregate Amount Beneficially Owned by Each Reporting Person <b>5,976,526</b>	
10.	Check if the Aggregate Amount in Row (9) Excludes Certain Shares <input type="checkbox"/>	
11.	Percent of Class Represented by amount in Row (9) <b>5.1%</b>	
12.	Type of Reporting Person (See Instructions) <b>HC,CO</b>	

1.	Names of Reporting Persons <b>Biotech Target N.V.</b> I.R.S. Identification Nos. of above persons (entities only): <b>N/A</b>	
2.	Check the Appropriate Box if a Member of a Group (See Instructions) (a) <input checked="" type="checkbox"/> (b) <input type="checkbox"/>	
3.	SEC Use Only	
4.	Citizenship or Place of Organization <b>Curacao</b>	
Number of Shares Beneficially Owned by Each Reporting Person with:	5.	Sole Voting Power <b>0</b>
	6.	Shared Voting Power <b>5,976,526</b>
	7.	Sole Dispositive Power <b>0</b>
	8.	Shared Dispositive Power <b>5,976,526</b>
9.	Aggregate Amount Beneficially Owned by Each Reporting Person <b>5,976,526</b>	
10.	Check if the Aggregate Amount in Row (9) Excludes Certain Shares <input type="checkbox"/>	
11.	Percent of Class Represented by amount in Row (9) <b>5.1%</b>	
12.	Type of Reporting Person (See Instructions) <b>CO</b>	

#### Item 4. Ownership

Provide the following information regarding the aggregate number and percentage of the class of securities of the issuer identified in Item 1.

- (a) Amount beneficially owned: 5,976,526
- (b) Percent of class: 5.1%
- (c) Number of shares as to which the person has:
  - (i) Sole power to vote or to direct the vote 0
  - (ii) Shared power to vote or to direct the vote 5,976,526
  - (iii) Sole power to dispose or to direct the disposition of 0
  - (iv) Shared power to dispose or to direct the disposition of 5,976,526



**Exhibit Index**

Exhibit A: Agreement by and between BB Biotech AG and Biotech Target N.V. with respect to the filing of this disclosure statement.\*

\*Previously filed as an exhibit to BB Biotech AG and Biotech Target N.V.'s Schedule 13G filed with the Securities and Exchange Commission on July 20, 2011.