

CERTIFICATE OF AMENDMENT TO THE RESTATED CERTIFICATE OF INCORPORATION

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

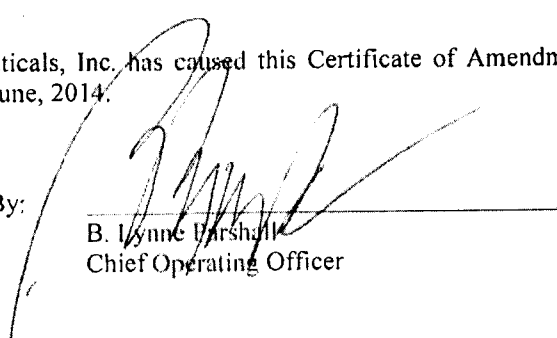
THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on February 11, 2014 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 315,000,000 shares, consisting of 300,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this 13th day of June, 2014.

By:


B. Lynne Marshall
Chief Operating Officer

RESTATED CERTIFICATE OF INCORPORATION
OF
ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under the General Corporation Law of the State of Delaware, does hereby certify as follows:

FIRST: The name of the corporation is Isis Pharmaceuticals, Inc.

SECOND: The Certificate of Incorporation of the corporation was filed by the Secretary of State on March 25, 1991.

THIRD: The Restated Certificate of Incorporation of the corporation, in the form attached hereto as Exhibit A, has been duly adopted in accordance with the provisions of Section 245 of the General Corporation Law of the State of Delaware by the Board of Directors of the corporation.

FOURTH: Pursuant to Section 245 of the Delaware General Corporation Law, approval of the stockholders of the corporation is not required.

FIFTH: The Restated Certificate of Incorporation so adopted reads in full as set forth in Exhibit A attached hereto and hereby incorporated by reference.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Restated Certificate of Incorporation to be signed by its President and attested to by its Assistant Secretary this 31st day of May 1991.

ISIS PHARMACEUTICALS, INC.

By


Stanley T. Crooke
President

ATTEST:

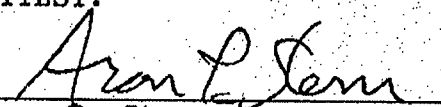

Aron P. Stern
Assistant Secretary

EXHIBIT A

RESTATED CERTIFICATE OF INCORPORATION
OF
ISIS PHARMACEUTICALS, INC.

I.

The name of the Corporation is Isis Pharmaceuticals, Inc.

II.

The address of the registered office of the Corporation in the State of Delaware is 32 Lookerman Square, Suite L-100, City of Dover, County of Kent, and the name of the registered agent of the Corporation in the State of Delaware at such address is The Prentice-Hall Corporation System, Inc.

III.

The purpose of the Corporation is to engage in any lawful act or activity for which a Corporation may be organized under the General Corporation Law of Delaware.

IV.

(a) The liability of the directors of the Corporation for monetary damages shall be eliminated to the fullest extent permissible under Delaware law.

(b) The Corporation is authorized to provide indemnification of agents (as defined in Section 145 of the Delaware General Corporation Law) for breach of duty to the Corporation and its stockholders through bylaw provisions, through agreements with the agents, and/or through stockholder resolutions, or otherwise, in excess of the indemnification otherwise permitted by Section 145 of the Delaware General Corporation Law, subject to the limitations on such excess indemnification set forth in Section 102 of the Delaware General Corporation Law.

(c) Any repeal or modification of this Article IV shall be prospective and shall not affect the rights under this Article IV in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

V.

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 65,000,000 shares, consisting of 50,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

VI.

For the management of the business and for the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

Section 1. Board of Directors.

(a) Management of Corporation. The management of the business and the conduct of the affairs of the Corporation shall be vested in its Board of Directors. The number of directors which shall constitute the whole Board of Directors shall be fixed exclusively by one or more resolutions adopted from time to time by the Board of Directors.

(b) Classified Board. Following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "1933 Act"), covering the offer and sale of Common Stock to the public (the "Initial Public Offering"):

(i) Designation of Classes. The directors shall be divided with respect to the time for which they generally hold office into three classes designated as Class I, Class II and Class III. Class I shall consist of two directors, with Class II and Class III consisting of three directors each. At the first annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

(ii) Change in Directorships. In case of any increase in the number of directorships, the additional directorships so created shall be classified so that, as nearly as possible, each class shall consist of one third of the number of directors then constituting the whole board. Newly created directorships resulting from any increase in the number of directors shall, unless the Board of Directors determines by resolution that any such newly created directorship shall be filled by the stockholders, be filled only by the affirmative vote of the directors then in office, even though less than a quorum of the Board of Directors. Any director elected in accordance with the preceding sentence shall serve until the next election of the class to which such additional directorship shall have been assigned. Notwithstanding the requirement that the three classes shall be as nearly equal in the number of directorships as possible, no change in the number of directorships shall operate to prevent a director then in office from continuing to serve as such until the expiration of his term or his earlier death, resignation or removal.

(iii) Modification of Section 1(b). Notwithstanding any other provisions of this Certificate of Incorporation (other than the provision for the change in the number of directorships set forth in Section 1(b)(ii)) or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock (as defined in Section 1(a) of Article VII) required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together

as a single class, shall be required to alter, amend or repeal this Section 1(b).

(c) Removal. Subject to any limitations imposed by law, the Board of Directors or any individual director may be removed from office at any time (i) with cause by the affirmative vote of the holders of at least a majority of the outstanding Voting Stock; or (ii) without cause by the affirmative vote of the holders of at least 66-2/3% of the outstanding Voting Stock.

Section 2. General.

(a) The Board of Directors may from time to time make, amend, supplement or repeal the Bylaws; provided, however, that the stockholders may change or repeal any Bylaw adopted by the Board of Directors by the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the capital stock of the Corporation (considered for this purpose as one class); and, provided further, that no amendment or supplement to the Bylaws adopted by the Board of Directors shall vary or conflict with any amendment or supplement thus adopted by the stockholders.

(b) The directors of the Corporation need not be elected by written ballot unless the Bylaws so provide.

(c) Following the closing of the Initial Public Offering, no action shall be taken by the stockholders of the Corporation except at an annual or special meeting of stockholders called in accordance with the Bylaws and no action shall be taken by the stockholders by written consent.

(d) Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the Corporation shall be given in the manner provided in the Bylaws of the Corporation.

VII.

Following the closing of the Initial Public Offering:

Section 1. Stockholder Vote Required for Business Combinations.

(a) Stockholder Votes. In addition to any affirmative vote required by law or by this Certificate of Incorporation or by any Preferred Stock Designation, and except as otherwise expressly provided in Section 2 of this Article VII:

(i) any merger or consolidation of the Corporation or any Subsidiary (as hereinafter defined) with

(A) any Interested Stockholder (as hereinafter defined) or
(B) any other corporation (whether or not itself an Interested Stockholder) which is, or after such merger or consolidation would be, an Affiliate (as hereinafter defined) of an Interested Stockholder; or

(ii) any sale, lease, exchange, mortgage, pledge, transfer or other disposition (in one transaction or a series of transactions) to or with any Interested Stockholder or any Affiliate of any Interested Stockholder of any assets of the Corporation or any Subsidiary having an aggregate Fair Market Value (as hereinafter defined) equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements; or

(iii) the issuance or transfer by the Corporation or any Subsidiary (in one transaction or a series of transactions) of any securities of the Corporation or any Subsidiary to any Interested Stockholder or any Affiliate of any Interested Stockholder in exchange for cash, securities or other property (or a combination thereof) having an aggregate Fair Market Value equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements; or

(iv) the adoption of any plan or proposal for the liquidation or dissolution of the Corporation proposed by or on behalf of any Interested Stockholder or any Affiliate of any Interested Stockholder; or

(v) any reclassification of securities (including any reverse stock split), or recapitalization of the Corporation, or any merger or consolidation of the Corporation with any of its Subsidiaries or any other transaction (whether or not with or into or otherwise involving any Interested Stockholder) which has the effect, directly or indirectly, of increasing the proportionate share of the outstanding shares of any class of equity or convertible securities of the Corporation or any Subsidiary which is Beneficially Owned (as hereinafter defined) by any Interested Stockholder or any Affiliate of any Interested Stockholder;

shall require the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of capital stock of the Corporation entitled to vote generally in the election of directors (the "Voting Stock"), voting together as a single class. Such affirmative vote shall be required notwithstanding any other provisions of this Certificate of

Incorporation or any provision of law or of any agreement with any national securities exchange or otherwise which might otherwise permit a lesser vote or no vote.

(b) Definition of Business Combination. The term "Business Combination" as used in this Article VII shall mean any transaction which is referred to in any one or more of subparagraphs (i) through (v) of paragraph (a) of this Section 1.

Section 2. Exceptions to Stockholder Vote Requirement.

The provisions of Section 1 of this Article VII shall not be applicable to any particular Business Combination, and such Business Combination shall require only such affirmative vote as is required by law and any other provision of this Certificate of Incorporation and any Preferred Stock Designation, if, in the case of a Business Combination that does not involve any cash or other consideration being received by the stockholders of the Corporation, solely in their respective capacities as stockholders of the Corporation, the condition specified in the following paragraph (a) is met, or, in the case of any other Business Combination, the conditions specified in either of the following paragraph (a) or paragraph (b) are met:

(a) The Business Combination shall have been approved by a majority of the Continuing Directors (as hereinafter defined); provided however, that this condition shall not be capable of satisfaction unless there are at least two Continuing Directors.

(b) All of the following conditions shall have been met:

(i) The consideration to be received by holders of shares of a particular class (or series) of outstanding capital stock of the Corporation (including Common Stock and other than Excluded Preferred Stock (as hereinafter defined)) shall be in cash or in the same form as the Interested Stockholder or any of its Affiliates has previously paid for shares of such class (or series) of capital stock. If the Interested Stockholder or any of its Affiliates have paid for shares of any class (or series) of capital stock with varying forms of consideration, the form of consideration to be received per share by holders of shares of such class (or series) of capital stock shall be either cash or the form used to acquire the largest number of shares of such class (or series) of capital stock previously acquired by the Interested Stockholder.

(ii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the date (the "Consummation Date") of the consummation of the Business Combination, of the consideration other than cash to be received per share by holders

of Common Stock in such Business Combination shall be at least equal to the higher of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the Interested Stockholder or any of its Affiliates for any shares of Common Stock acquired by them within the two-year period immediately prior to the date of the first public announcement of the proposal of the Business Combination (the "Announcement Date") or in any transaction in which the Interested Stockholder became an Interested Stockholder, whichever is higher, plus interest compounded annually from the first date on which the Interested Stockholder became an Interested Stockholder (the "Determination Date") through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T. & S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of Common Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of Common Stock; and

(B) the Fair Market Value per share of Common Stock on the Announcement Date or the Determination Date, whichever is higher.

(iii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the Consummation Date, of the consideration other than cash to be received per share by holders of shares of any class (or series), other than Common Stock or Excluded Preferred Stock, of outstanding Voting Stock shall be at least equal to the higher of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event), it being intended that the requirements of this paragraph (b)(iii) shall be required to be met with respect to every such class (or series) of outstanding Voting Stock whether or not the Interested Stockholder or any of its Affiliates has previously acquired any shares of a particular class (or series) of Voting Stock):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the

Interested Stockholder or any of its Affiliates for any shares of such class (or series) of Voting Stock acquired by them within the two-year period immediately prior to the Announcement Date or in any transaction in which it became an Interested Stockholder, whichever is higher, plus interest compounded annually from the Determination Date through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T. & S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of such class (or series) of Voting Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of such class (or series) of Voting Stock;

(B) the Fair Market Value per share of such class (or series) of Voting Stock on the Announcement Date or on the Determination Date, whichever is higher; and

(C) the highest preferential amount per share, if any, to which the holders of shares of such class (or series) of Voting Stock would be entitled in the event of any voluntary or involuntary liquidation, dissolution or winding up of the corporation.

(iv) After such Interested Stockholder has become an Interested Stockholder and prior to the consummation of such Business Combination: (x) except as approved by a majority of the Continuing Directors, there shall have been no failure to declare and pay at the regular date therefor any full quarterly dividends (whether or not cumulative) on any outstanding Preferred Stock; (y) there shall have been (A) no reduction in the annual rate of dividends paid on the Common Stock (except as necessary to reflect any subdivision of the Common Stock), except as approved by a majority of the Continuing Directors, and (B) an increase in such annual rate of dividends as necessary to reflect any reclassification (including any reverse stock split), recapitalization, reorganization or any similar transaction which has the effect of reducing the number of outstanding shares of the Common Stock, unless the failure so to increase such annual rate is approved by a majority of the Continuing Directors; and (z) neither such Interested Stockholder nor any of its Affiliates shall have become the beneficial owner of any additional shares of Voting Stock except as part of the transaction which results in such Interested Stockholder becoming an Interested Stockholder; provided, however, that no approval by

Continuing Directors shall satisfy the requirements of this subparagraph (iv) unless at the time of such approval there are at least two Continuing Directors.

(v) After such Interested Stockholder has become an Interested Stockholder, such Interested Stockholder and any of its Affiliates shall not have received the benefit, directly or indirectly (except proportionately, solely in such Interested Stockholder's or Affiliate's capacity as a stockholder of the Corporation), of any loans, advances, guarantees, pledges or other financial assistance or any tax credits or other tax advantages provided by the Corporation, whether in anticipation of or in connection with such Business Combination or otherwise.

(vi) A proxy or information statement describing the proposed Business Combination and complying with the requirements of the Securities Exchange Act of 1934, as amended (the "1934 Act") and the rules and regulations thereunder (or any subsequent provisions replacing such Act, rules or regulations) shall be mailed to all stockholders of the Corporation at least 30 days prior to the consummation of such Business Combination (whether or not such proxy or information statement is required to be mailed pursuant to such Act or subsequent provisions).

(vii) Such Interested Stockholder shall have supplied the Corporation with such information as shall have been requested pursuant to Section 5 of this Article VII within the time period set forth therein.

Section 3. Definitions.

For the purposes of this Article VII:

(a) A "person" means any individual, limited partnership, general partnership, corporation or other firm or entity.

(b) "Interested Stockholder" means any person (other than the Corporation or any Subsidiary) who or which:

(i) is the Beneficial Owner (as hereinafter defined), directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(ii) is an Affiliate of the Corporation and at any time within the two-year period immediately prior to the date in question was the Beneficial Owner, directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(iii) is an assignee of or has otherwise succeeded to any shares of Voting Stock which were at any time within the

two-year period immediately prior to the date in question Beneficially Owned by an Interested Stockholder, if such assignment or succession shall have occurred in the course of a transaction or series of transactions not involving a public offering within the meaning of the 1933 Act.

(c) A person shall be a "Beneficial Owner" of or shall "Beneficially Own" any Voting Stock:

(i) which such person or any of its Affiliates or Associates (as hereinafter defined) beneficially owns, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on March 14, 1988; or

(ii) which such person or any of its Affiliates or Associates has (A) the right to acquire (whether such right is exercisable immediately or only after the passage of time), pursuant to any agreement, arrangement or understanding or upon the exercise of conversion rights, exchange rights, warrants or options, or otherwise, or (B) the right to vote pursuant to any agreement, arrangement or understanding (but shall not be deemed to be the beneficial owner of any shares of Voting Stock solely by reason of a revocable proxy granted for a particular meeting of stockholders, pursuant to a public solicitation of proxies for such meeting, and with respect to which shares neither such person nor any such Affiliate or Associate is otherwise deemed the beneficial owner); or

(iii) which is beneficially owned, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation, by any other person with which such person or any of its Affiliates or Associates has any agreement, arrangement or understanding for the purpose of acquiring, holding, voting (other than solely by reason of a revocable proxy as described in subparagraph (ii) of this paragraph (c)) or disposing of any shares of Voting Stock;

provided, however, that in case of any employee stock ownership or similar plan of the Corporation or of any Subsidiary in which the beneficiaries thereof possess the right to vote any shares of Voting Stock held by such plan, no such plan nor any trustee with respect thereto (nor any Affiliate of such trustee), solely by reason of such capacity of such trustee, shall be deemed, for any purposes hereof, to Beneficially Own any shares of Voting Stock held under any such plan.

(d) For the purposes of determining whether a person is an Interested Stockholder pursuant to paragraph (b) of this Section 3, the number of shares of Voting Stock deemed to be outstanding shall include shares deemed Beneficially Owned through application of paragraph (c) of this Section 3 but shall

not include any other unissued shares of Voting Stock which may be issuable pursuant to any agreement, arrangement or understanding, or upon exercise of conversion rights, warrants or options, or otherwise.

(e) "Affiliate" or "Associate" shall have the respective meanings ascribed to such terms in Rule 12b-2 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation.

(f) "Subsidiary" means any corporation of which a majority of the outstanding shares of any class of equity security is owned, directly or indirectly, by the Corporation; provided, however, that for the purposes of the definition of Interested Stockholder set forth in paragraph (b) of this Section 3, the term "Subsidiary" shall mean only a corporation of which a majority of the outstanding shares of each class of equity security is owned, directly or indirectly, by the Corporation.

(g) "Continuing Director" means a member of the Board of Directors of the Corporation who is originally elected upon the incorporation of the Corporation or who is not an Interested Stockholder or affiliated with an Interested Stockholder or in connection with his or her initial assumption of office is recommended and approved for an appointment or election by a majority of Continuing Directors then on the Board.

(h) "Fair Market Value" means: (i) in the case of stock, the highest closing sale price during the 30-day period immediately preceding the date in question of a share of such stock on the Composite Tape for New York Stock Exchange-Listed Stocks, or, if such stock is not quoted on the Composite Tape, on the New York Stock Exchange, or, if such stock is not listed on such Exchange, on the principal United States securities exchange registered under the 1934 Act on which such stock is listed, or, if such stock is not listed on any such exchange, the highest closing sale price quotation with respect to a share of such stock during the 30-day period preceding the date in question on the National Association of Securities Dealers, Inc. Automated Quotations System or any system then in use, or if no such quotations are available, the fair market value on the date in question of a share of such stock as determined by the Board in accordance with Section 4 of this Article VII; and (ii) in the case of property other than cash or stock, the fair market value of such property on the date in question as determined by the Board in accordance with Section 4 of this Article VII.

(i) In the event of any Business Combination in which the Corporation survives, the phrase "consideration other than cash to be received" as used in paragraphs (b)(ii) and (b)(iii) of Section 2 of this Article VII shall include the shares of

Common Stock and/or the shares of any other class (or series) of outstanding Voting Stock retained by the holders of such shares.

(j) "Whole Board" means the total number of directors which this corporation would have if there were no vacancies.

(k) "Excluded Preferred Stock" means any series of Preferred Stock with respect to which the Preferred Stock Designation creating such series expressly provides that the provisions of this Article VII shall not apply.

Section 4. Board Enforcement.

(a) Compliance. A majority of the Whole Board but only if a majority of the Whole Board shall then consist of Continuing Directors or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors, shall have the power and duty to determine, on the basis of information known to them after reasonable inquiry, all facts necessary to determine compliance with this Article VII, including, without limitation, (i) whether a person is an Interested Stockholder, (ii) the number of shares of Voting Stock beneficially owned by any person, (iii) whether a person is an Affiliate or Associate of another, (iv) whether the applicable conditions set forth in paragraph (b) of Section 2 have been met with respect to any Business Combination, (v) the Fair Market Value of stock or other property in accordance with paragraph (h) of Section 3, and (vi) whether the assets which are the subject of any Business Combination referred to in paragraph (a)(ii) of Section 1 have or the consideration to be received for the issuance or transfer of securities by the Corporation or any Subsidiary in any Business Combination referred to in paragraph (a)(iii) of Section 1 has, an aggregate Fair Market Value equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements.

(b) Demand as to Interested Stockholder. A majority of the Whole Board shall have the right to demand, but only if a majority of the Whole Board shall then consist of Continuing Directors, or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors shall have the right to demand, that any person who it is reasonably believed is an Interested Stockholder (or holds of record shares of Voting Stock Beneficially Owned by any Interested Stockholder) supply this Corporation with complete information as to (i) the record owner(s) of all shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder, (ii) the number of, and class or series of, shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder and held of record by each such record owner and the number(s) of the stock

certificate(s) evidencing such shares, and (iii) any other factual matter relating to the applicability or effect of this Article VII, as may be reasonably requested of such person, and such person shall furnish such information within 10 days after receipt of such demand.

(c) Fiduciary Obligation of Interested Stockholder. Nothing contained in this Article VII shall be construed to relieve any Interested Stockholder from any fiduciary obligation imposed by law.

(d) Modification of Article VII. Notwithstanding any other provisions of this Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal this Article VII.

VIII.

No holder of shares of stock of the Corporation shall have any preemptive or other right, except as such rights are expressly provided by contract, to purchase or subscribe for or receive any shares of any class, or series thereof, of stock of the Corporation, whether now or hereafter authorized, or any warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any share of any class, or series thereof, of stock; but such additional shares of stock and such warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any shares of any class, or series thereof, of stock may be issued or disposed of by the Board of Directors to such persons, and on such terms and for such lawful consideration, as in its discretion it shall deem advisable or as the Corporation shall have by contract agreed.

**CERTIFICATE OF DESIGNATION
OF
SERIES C JUNIOR PARTICIPATING PREFERRED STOCK**

**(Pursuant to Section 151 of the
Delaware General Corporation Law)**

ISIS PHARMACEUTICALS, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware (hereinafter called the "Company"), hereby certifies that the following resolution was adopted by the Board of Directors of the Corporation as required by Section 151 of the General Corporation Law at a meeting duly called and held on December 8, 2000:

RESOLVED, that pursuant to the authority granted to and vested in the Board of Directors of the Company in accordance with the provisions of its Restated Certificate of Incorporation, the Board of Directors hereby creates a series of Preferred Stock, par value \$.001 per share, of the Company and hereby states the designation and number of shares, and fixes the relative designations and the powers, preferences and rights, and the qualifications, limitations and restrictions thereof (in addition to the provisions set forth in the Restated Certificate of Incorporation of the Company, which are applicable to the Preferred Stock of all classes and series), as follows:

Series C Junior Participating Preferred Stock:

Section 1. Designation and Amount. One million (1,000,000) shares of Preferred Stock, \$.001 par value, are designated "Series C Junior Participating Preferred Stock" with the designations and the powers, preferences and rights, and the qualifications, limitations and restrictions specified herein (the "Junior Preferred Stock"). Such number of shares may be increased or decreased by resolution of the Board of Directors; *provided*, that no decrease shall reduce the number of shares of Junior Preferred Stock to a number less than the number of shares then outstanding plus the number of shares reserved for issuance upon the exercise of outstanding options, rights or warrants or upon the conversion of any outstanding securities issued by the Company convertible into Junior Preferred Stock.

Section 2. Dividends and Distributions.

(A) Subject to the rights of the holders of any shares of any series of Preferred Stock (or any similar stock) ranking prior and superior to the Junior Preferred Stock with respect

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to dividends, the holders of shares of Junior Preferred Stock, in preference to the holders of Common Stock, par value \$.001 per share (the "Common Stock"), of the Company, and of any other junior stock, shall be entitled to receive, when, as and if declared by the Board of Directors out of funds legally available for the purpose, quarterly dividends payable in cash on the first day of April, July, October and January in each year (each such date being referred to herein as a "Quarterly Dividend Payment Date"), commencing on the first Quarterly Dividend Payment Date after the first issuance of a share or fraction of a share of Junior Preferred Stock, in an amount per share (rounded to the nearest cent) equal to the greater of (a) \$1.00 or (b) subject to the provision for adjustment hereinafter set forth, 100 times the aggregate per share amount of all cash dividends, and 100 times the aggregate per share amount (payable in kind) of all non-cash dividends or other distributions, other than a dividend payable in shares of Common Stock or a subdivision of the outstanding shares of Common Stock (by reclassification or otherwise), declared on the Common Stock since the immediately preceding Quarterly Dividend Payment Date or, with respect to the first Quarterly Dividend Payment Date, since the first issuance of any share or fraction of a share of Junior Preferred Stock. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event under clause (b) of the preceding sentence shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) The Company shall declare a dividend or distribution on the Junior Preferred Stock as provided in paragraph (A) of this Section immediately after it declares a dividend or distribution on the Common Stock (other than a dividend payable in shares of Common Stock); *provided*, that in the event no dividend or distribution shall have been declared on the Common Stock during the period between any Quarterly Dividend Payment Date and the next subsequent Quarterly Dividend Payment Date, a dividend of \$1.00 per share on the Junior Preferred Stock shall nevertheless be payable on such subsequent Quarterly Dividend Payment Date.

(C) Dividends shall begin to accrue and be cumulative on outstanding shares of Junior Preferred Stock from the Quarterly Dividend Payment Date next preceding the date of issue of such shares, unless the date of issue of such shares is prior to the record date for the first Quarterly Dividend Payment Date, in which case dividends on such shares shall begin to accrue from the date of issue of such shares, or unless the date of issue is a Quarterly Dividend Payment Date or is a date after the record date for the determination of holders of shares of Junior Preferred Stock entitled to receive a quarterly dividend and before such Quarterly Dividend Payment Date, in either of which events such dividends shall begin to accrue and be cumulative from such Quarterly Dividend Payment Date. Accrued but unpaid dividends shall not bear interest. Dividends paid on the shares of Junior Preferred Stock in an amount less than the total amount of such dividends at the time accrued and payable on such shares shall be allocated pro rata on a share-by-share basis among all such shares at the time outstanding. The Board of Directors may fix a record date for the determination of holders of shares of Junior Preferred

Stock entitled to receive payment of a dividend or distribution declared thereon, which record date shall be not more than 60 days prior to the date fixed for the payment thereof.

Section 3. Voting Rights. The holders of shares of Junior Preferred Stock shall have the following voting rights:

(A) Subject to the provision for adjustment hereinafter set forth, each share of Junior Preferred Stock shall entitle the holder thereof to 100 votes on all matters submitted to a vote of the stockholders of the Company. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the number of votes per share to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event shall be adjusted by multiplying such number by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) Except as otherwise provided herein, in any other Certificate of Designation creating a series of Preferred Stock or any similar stock, or by law, the holders of shares of Junior Preferred Stock and the holders of shares of Common Stock and any other capital stock of the Company having general voting rights shall vote together as one class on all matters submitted to a vote of stockholders of the Company.

(C) Except as set forth herein, or as otherwise provided by law, holders of Junior Preferred Stock shall have no special voting rights and their consent shall not be required (except to the extent they are entitled to vote with holders of Common Stock as set forth herein) for taking any corporate action.

Section 4. Certain Restrictions.

(A) Whenever quarterly dividends or other dividends or distributions payable on the Junior Preferred Stock as provided in Section 2 are in arrears, thereafter and until all accrued and unpaid dividends and distributions, whether or not declared, on shares of Junior Preferred Stock outstanding shall have been paid in full, the Company shall not:

(i) declare or pay dividends, or make any other distributions, on any shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock;

(ii) declare or pay dividends, or make any other distributions, on any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except dividends paid ratably on the Junior Preferred Stock and all such parity stock on which dividends are payable or in arrears in proportion to the total amounts to which the holders of all such shares are then entitled;

(iii) redeem or purchase or otherwise acquire for consideration shares of any stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock, provided that the Company may at any time redeem, purchase or otherwise acquire shares of any such junior stock in exchange for shares of any stock of the Company ranking junior (either as to dividends or upon dissolution, liquidation or winding up) to the Junior Preferred Stock; or

(iv) redeem or purchase or otherwise acquire for consideration any shares of Junior Preferred Stock, or any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except in accordance with a purchase offer made in writing or by publication (as determined by the Board of Directors) to all holders of such shares upon such terms as the Board of Directors, after consideration of the respective annual dividend rates and other relative rights and preferences of the respective series and classes, shall determine in good faith will result in fair and equitable treatment among the respective series or classes.

(B) The Company shall not permit any subsidiary of the Company to purchase or otherwise acquire for consideration any shares of stock of the Company unless the Company could, under paragraph (A) of this Section 4, purchase or otherwise acquire such shares at such time and in such manner.

Section 5. Reacquired Shares. Any shares of Junior Preferred Stock purchased or otherwise acquired by the Company in any manner whatsoever shall be retired and cancelled promptly after the acquisition thereof. All such shares shall upon their cancellation become authorized but unissued shares of Preferred Stock and may be reissued as part of a new series of Preferred Stock subject to the conditions and restrictions on issuance set forth herein, in the Restated Certificate of Incorporation, or in any other Certificate of Designation creating a series of Preferred Stock or any similar stock or as otherwise required by law.

Section 6. Liquidation, Dissolution or Winding Up. Upon any liquidation, dissolution or winding up of the Company, no distribution shall be made (1) to the holders of shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock unless, prior thereto, the holders of shares of Junior Preferred Stock shall have received \$100 per share, plus an amount equal to accrued and unpaid dividends and distributions thereon, whether or not declared, to the date of such payment, or if greater, the holders of shares of Junior Preferred Stock shall be entitled to receive an aggregate amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount to be distributed per share to holders of shares of Common Stock; or (2) to the holders of shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except distributions made ratably on the Junior Preferred Stock and all such parity stock in proportion to the total amounts to which the holders of all such shares are entitled upon such liquidation, dissolution or winding up. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the aggregate amount to which holders of shares of Junior

Preferred Stock were entitled immediately prior to such event under the proviso in clause (1) of the preceding sentence shall be adjusted by multiplying such amount by a fraction the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 7. Consolidation, Merger, Etc. In case the Company shall enter into any consolidation, merger, combination or other transaction in which the shares of Common Stock are exchanged for or changed into other stock or securities, cash and/or any other property, then in any such case each share of Junior Preferred Stock shall at the same time be similarly exchanged or changed into an amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount of stock, securities, cash and/or any other property (payable in kind), as the case may be, into which or for which each share of Common Stock is changed or exchanged. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount set forth in the preceding sentence with respect to the exchange or change of shares of Junior Preferred Stock shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 8. No Redemption. The shares of Junior Preferred Stock shall not be redeemable.

Section 9. Rank. The Junior Preferred Stock shall rank, with respect to the payment of dividends and the distribution of assets, junior to all series of any other class of the Company's Preferred Stock.

Section 10. Amendment. The Restated Certificate of Incorporation of the Company shall not be amended in any manner which would materially alter or change the powers, preferences or special rights of the Junior Preferred Stock so as to affect them adversely without the affirmative vote of the holders of at least two-thirds of the outstanding shares of Junior Preferred Stock, voting together as a single class.

IN WITNESS WHEREOF, the undersigned have executed this certificate as of
December 12, 2000.

By: 

Print Name: **B. LYNNE PARSHALL**
Executive Vice President,
Chief Financial Officer and Secretary