

# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## FORM 8-K

### CURRENT REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): **November 6, 2002**

## ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

**Delaware**

(State or Other Jurisdiction of Incorporation)

**000-19125**

(Commission File No.)

**33-0336973**

(IRS Employer Identification No.)

**2292 Faraday Avenue  
Carlsbad, CA 92008**

(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

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#### Item 5. Other Events.

On November 6, 2002 we announced that we regained rights to ISIS 14803, in connection with the termination of our collaboration with Elan Corporation, plc. related to the HepaSense Ltd. joint venture. Additionally, we announced an agreement with Elan to amend the terms and extend our collaboration in the Orasense Ltd., joint venture through the end of 2002.

HepaSense was focused on the clinical development of the antisense drug ISIS 14803 for patients with Hepatitis C. As part of the termination, all rights to ISIS 14803 have been returned to Isis, with a potential royalty due to HepaSense.

Orasense is a joint venture to develop an oral delivery platform for antisense drugs, and to develop an oral formulation of ISIS 104838, an antisense inhibitor of TNF-alpha, for the treatment of rheumatoid arthritis. The collaboration will continue through the remainder of this year, with Isis and Elan contributing funding according to ownership, 80.1 percent and 19.9 percent, respectively. In 2003, Elan will have the option to extend or conclude its participation in the Orasense collaboration.

#### Item 7. Exhibits.

- 10.1\* Amended and Restated License Agreement among Orasense Ltd, Isis Pharmaceuticals, Inc. and Elan Corporation, Plc. dated October 24, 2002.
- 10.2\* Amended and Restated License Agreement among Orasense Ltd, Isis Pharmaceuticals, Inc. and Elan Corporation, Plc. dated October 24, 2002.
- 10.3\* Amended and Restated Subscription, Joint Development and Operating Agreement among Elan Corporation, Plc., Elan International Services, Ltd., Isis Pharmaceuticals, Inc. and Orasense Ltd. dated October 24, 2002.
- 10.4\* Termination Agreement among Elan Corporation, Plc., Elan Pharma International Limited, Elan International Services, Ltd., Isis Pharmaceuticals, Inc. and Hepasense Ltd. dated November 5, 2002.
- 99.1 Press Release dated November 6, 2002 regarding Elan Corporation, plc. and Isis Pharmaceuticals, Inc.

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\* Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.



Isis License Agreement  
Execution Copy (V7)  
24 October 2002

**AMENDED AND RESTATED  
LICENSE AGREEMENT**

**BY AND BETWEEN**

**ORASENSE LTD**

**A Bermuda Limited Company**

**ISIS PHARMACEUTICALS, INC**

**A Delaware Corporation**

**AND**

**ELAN CORPORATION, PLC**

**A Public Irish Company**

**October 24, 2002**

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**AMENDED AND RESTATED LICENSE AGREEMENT** made this 24<sup>th</sup> day of October, 2002 among, Isis Pharmaceuticals, Inc., a Delaware corporation, Elan Corporation, plc, Orasense Ltd. a Bermuda limited company.

**RECITALS:**

A. Contemporaneously herewith, Elan, EIS, Orasense and Isis (capitalized terms used herein are defined below) are entering into the Development Agreement for the purpose of amending, restating and recording the terms and conditions of a joint venture and of regulating their relationship with each other and certain aspects of the affairs of and their dealings with Orasense.

B. Isis is beneficially entitled to the use of certain know-how and certain patents that have been granted or are pending in relation to the development and production of various drug delivery technologies and drug products.

C. Orasense desires to enter into this Agreement with Isis so as to permit Orasense to utilize the Isis Intellectual Property in the research, development, manufacture, distribution and sale of Products in the Field and in the Territory.

D. Orasense and Isis entered into that certain License Agreement (the "Original License Agreement") dated April 20, 1999 (the "Original Effective Date"). The Parties now wish to amend, restate and supercede the Original License Agreement with this Agreement.

**NOW THEREFORE, IT IS HEREBY AGREED AS FOLLOWS:**

**1. DEFINITIONS; INTERPRETATION**

A. *Definitions.* In this Agreement, the following definitions shall apply:

1.1. "Affiliate" shall mean, with respect to Elan or Isis, any corporation or entity other than Orasense (and entities controlled by it) controlling, controlled or under the common control of Elan or Isis, as the case may be, and, with respect to Orasense, any corporation or entity under control of Orasense, but excluding, in the case of Elan, an Elan JV. A corporation or non-corporate entity shall be regarded as in control of another corporation if it owns or directly or indirectly controls at least fifty percent (50%) of the voting stock of the other corporation or (a) in the absence of the ownership of at least fifty percent (50%) of the voting stock of a corporation or (b) in the case of a non-corporate entity, the power to direct or cause the direction of the management and policies of such corporation or non-corporate entity, as applicable.

1.2. "Agreement" shall mean this agreement (which expression shall be deemed to include the Recitals and the Schedules hereto);

1.3. "cGCP", "cGLP" and "cGMP" shall mean current Good Clinical Practices, current Good Laboratory Practices and current Good Manufacturing Practices respectively;

1.4. "Commercialization" shall mean the manufacture, promotion, distribution, marketing and sale of the Products;

1.5. "Control" shall mean the ability of a Party to grant a license or sublicense as contemplated herein without having to obtain the prior consent of any third party or having to amend any agreement between such Party and a third party;

1.6. "Cost of Living Increase" shall mean, with respect to any year of the Term, any increase in the Consumer Price Index published by the Bureau of Labor Statistics of the United States Department of Labor, All Urban Consumers, United States City Average, All Items (1982-84=100);

1.7. "Development Agreement" shall mean the Amended and Restated Joint Development and Operating Agreement of even date entered into among Isis, Elan, EIS and Orasense;

1.8. "Development Candidate" shall mean ISIS 104838 [\*\*\*] of TNF-a, as more specifically detailed in Exhibit A hereto;

1.9. "Development Product" shall mean any product containing as an active ingredient the Development Candidate formulated using the Oral Platform for humans;

1.10. "Effective Date" shall mean the date of execution and delivery of this Agreement;

1.11. "EIS" shall mean Elan International Services, Ltd., a Bermuda limited company;

1.12. "Elan" shall mean Elan Corporation, plc, a public limited company incorporated under the laws of Ireland, its, successors and permitted assigns;

1.13. "Elan Intellectual Property" shall have the meaning set forth in the Elan License Agreement;

1.14. "Elan JV" shall mean an entity that Elan and a third party (i) establish or have established; (ii) take shareholdings in or have a right to take shareholdings in; and (iii) grant certain licenses in and to certain intellectual property rights for the purpose of implementing a strategic alliance;

1.15. "Elan License" shall have the meaning set forth in Clause 2.1 of the Elan License Agreement;

- 1.16. "Elan License Agreement" shall mean that certain amended and restated license agreement between Isis, Orasense and Elan of even date herewith;
- 1.17. "Excluded Isis Technology" shall mean any Isis oligonucleotide chemistry technology including, without limitation, modified heterocycles, sugars or backbone linkages or conjugation technology;
- 1.18. "Failure to Fund" shall have the meaning set forth under Clause 9 of the Development Agreement;
- 1.19. "FDA" shall mean the United States Food and Drug Administration or any successors or agency the approval of which is necessary to market a product in the United States of America;
- 1.20. "Field" shall mean the research, development and Commercialization of the Oral Platform for use with Oligonucleotide Drugs;
- 1.21. "Full Time Equivalent Rate" shall mean, for the services proposed to be rendered by Isis [\*\*\*];
- 1.22. "Independent Third Party" shall mean any person other than Orasense, Elan, Isis or any of their respective Affiliates;
- 1.23. "Isis" shall mean Isis Pharmaceuticals, Inc., a Delaware corporation, its successors and permitted assigns;
- 1.24. "Isis Delivery Technology" shall mean (a) Patents Controlled by Isis claiming inventions made on or before the end of the Research Term and (b) Know-How Controlled by Isis through the end of the Research Term, that are necessary to practice within the Field;
- 1.25. "Isis Development Candidate Technology" shall mean Patents and/or Know-How Controlled by Isis which are necessary or useful for the manufacture or Commercialization of the Development Product;
- 1.26. "Isis Intellectual Property" shall mean the Isis Delivery Technology and the Isis Development Candidate Technology. For the avoidance of doubt, Isis Intellectual Property shall exclude the Excluded Isis Technology and Orasense Collaboration Intellectual Property;

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- 1.27. "Isis License" shall mean the Isis Drug Delivery License and the Isis Development Candidate License together.
- 1.28. "Isis License Agreement" shall mean this Agreement;
- 1.29. "Know-How" shall mean any and all rights to any discovery, invention (whether or not patentable), know-how, substances, data, techniques, processes, systems, formulations and designs which is not generally known to the public;
- 1.30. "Label", "Labeled" or "Labeling" shall mean all labels and other written, printed or graphic matter upon (i) the Product or any container or wrapper utilized with the Product, or (ii) any written material accompanying the Product, including, without limitation, package inserts;
- 1.31. "Licensed Technologies" shall mean the Elan Intellectual Property and the Isis Intellectual Property;
- 1.32. "Licenses" shall mean the Elan License and the Isis License;
- 1.33. "Lien" shall mean any and all liens, security interests, restrictions, claims, encumbrances or rights of third parties of every kind and nature;
- 1.34. "Management Committee" shall have the meaning given to such term in the Development Agreement;
- 1.35. "Marketing Authorization" shall mean any and all consents or other authorizations or approvals required from a Regulatory Authority or other governmental authority to Commercialize a pharmaceutical product in a country in the Territory;
- 1.36. "Net Sales" shall mean [\*\*\*]
- 1.37. "Oligonucleotide Drug" shall mean any single stranded, [\*\*\*] at physiological pH oligonucleotide including those [\*\*\*] used as a human therapeutic and/or prophylactic compound containing between [\*\*\*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [\*\*\*]. For purposes of this agreement, Oligonucleotide Drug shall specifically exclude oligonucleotides used in [\*\*\*], oligonucleotides used as [\*\*\*] an oligonucleotide, oligonucleotides used [\*\*\*] or oligonucleotides used as [\*\*\*];
- 1.38. "Oral Platform" shall mean formulation and excipient systems and technologies [\*\*\*] which use [\*\*\*] to develop dosage forms of drugs and deliver said dosage forms to the [\*\*\*] to achieve a local or systemic therapeutic effect;
- 1.39. "Orasense" shall mean Orasense, Ltd., a Bermuda limited company, its successors and permitted assigns;
- 1.40. "Orasense Collaboration Intellectual Property" shall mean (a) Know-How Controlled by Orasense through the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made on or before the end of the Research Term, and/or (c) inventions and Patents issued thereon developed by Orasense, Isis and/or Elan on behalf of Orasense (or any third party under contract with Orasense, Isis and/or Elan) or otherwise under the Original Research Plan or the Research Plan. Schedule 2 to this Agreement shall contain, by way of illustration but not limitation, examples of Orasense Collaboration Intellectual Property. At the end of the Research Term, the Parties shall amend Schedule 2 as may be necessary. For the avoidance of doubt, Orasense Collaboration Intellectual Property does not include any Patents and Know-How Controlled by Elan or Isis, as the case may be
- 1.41. "Orasense Intellectual Property" shall mean Orasense Collaboration Intellectual Property and Orasense Post Collaboration Intellectual Property;

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1.42. "Orasense Post-Collaboration Intellectual Property" shall mean (a) Know-How Controlled by Orasense after the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made after the end of the Research Term, and/or (c) inventions and Patents issued thereon made by Isis on Orasense's behalf after a Failure to Fund. For the avoidance of doubt, Orasense Post-Collaboration Intellectual Property does not include any Patents and Know-How Controlled by Elan or Isis, as the case may be;

1.43. "Original Research Plan" means the Research and Development Program under that certain Subscription, Joint Development and Operating Agreement between Elan, EIS, Isis and Orasense dated April 20, 1999;

1.44. "Package", "Packaged" and "Packaging" shall mean all primary and secondary packaging components, including, without limitation, cartons, partitions, shippers or any other like matter used in packaging the Product;

1.45. "Parties" shall mean Elan, Isis and Orasense and "Party" shall mean Elan, Isis or Orasense;

1.46. "Patents" shall mean any and all patents and patent applications under the Control of a Party hereto. Patents shall also include all extensions, continuations, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts of such patents and patent applications and any patents issuing thereon and extensions of any patents licensed hereunder;

1.47. "Person" shall mean an individual, partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture, or other entity of whatever nature;

1.48. "Product" shall mean any drug under development or developed by or on behalf of Orasense made or formulated using the Isis Delivery Technology, the Elan Intellectual Property and/or the Orasense Intellectual Property for administration to humans;

1.49. "Regulatory Application" shall mean a regulatory application or other application (including any supplements or amendments thereto) required to be filed or filed with a Regulatory Authority in a country in connection with the Commercialization of a pharmaceutical product in such country.

1.50. "Regulatory Authority" shall mean any regulatory authority outside the United States of America, the approval of which is necessary to market a Product;

1.51. "Research Plan" shall have the meaning set forth in the Development Agreement;

1.52. "Research Term" shall mean the period commencing on [\*\*\*] and continuing through [\*\*\*], and any extension thereto by the mutual agreement of Isis and Elan;

1.53. "Term" shall have the meaning set forth in Clause 12 below;

1.54. "Territory" shall mean all the countries of the world;

1.55. "United States Dollar" and "US\$" shall mean the lawful currency for the time being of the United States of America;

B. *Interpretation.* In this Agreement the following shall apply:

(1) The singular includes the plural and vice versa, the masculine includes the feminine and vice versa.

(2) Any reference to a Clause or Schedule shall, unless otherwise specifically provided, be to a Clause or Schedule of this Agreement.

(3) The headings of this Agreement are for ease of reference only and shall not affect its construction or interpretation.

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## 2. GRANT OF RIGHTS.

2.1. Subject to the terms and conditions contained herein and, in consideration of the payments specified under Clause 6.1, Isis hereby grants to Orasense for the Term a non-exclusive license, including the limited right to grant sublicenses pursuant to Clause 2.5 hereof, in the Field in the Territory to the Isis Delivery Technology to research, develop, make and have made, offer for sale, sell, import and export the Products and the Oral Platform in the Field, subject to any contractual obligations of Isis to Independent Third Parties as of the Effective Date and, unless prohibited by the paragraph below titled *Non Competition*, contractual obligations to Independent Third Parties that Isis may enter into after the Effective Date (the "Isis Drug Delivery License");

2.2. Subject to the terms and conditions contained herein and, in consideration of the payments specified under Clause 6.1, Isis hereby grants to Orasense for the Term an exclusive license in the Territory to the Isis Development Candidate Technology to manufacture and Commercialize the Development Product, subject to any contractual obligations of Isis to Independent Third Parties as of the Effective Date (the "Isis Development Candidate License").

2.3. In the event, the Isis License granted to Orasense hereunder is restricted or limited by any contractual obligations of Isis or rights of any Independent Third Parties (a) at any time after the Effective Date or (b) as a result of a breach of the noncompetition provision under Clause 11 of the Original License Agreement, Isis shall use reasonable commercial efforts to exclude or, where applicable, to minimize any such restriction or limitation. Except as expressly provided herein, all proprietary rights and rights of ownership with respect to the Isis Intellectual Property shall at all times remain solely with Isis. For the avoidance of doubt, Isis shall not have any obligations to exclude or minimize any restrictions or limitations under any agreement between an Independent Third Party and Isis entered into prior to the Effective Date, unless such restrictions or limitations arise in connection with a breach by Isis of the noncompetition provision under Clause 11 of the Original License Agreement.

To the extent royalty or other compensation obligations to Independent Third Parties that are payable with respect to Isis Intellectual Property would be triggered by the use or proposed use of Isis Intellectual Property by Orasense, its Affiliates and/or sublicensees, Isis will inform Orasense and Elan of such royalty or compensation obligation. If Orasense decides to utilize the Isis Intellectual Property, then Orasense will be responsible for the payment of such royalty or other compensation obligations relating thereto.

2.4. Notwithstanding anything contained in this Agreement to the contrary, Isis shall have the right, and subject to the paragraph below titled Non-Competition, to fully exploit and grant licenses and sublicenses with respect to the Isis Delivery Technology. Isis's rights to exploit and grant licenses referred to in the immediately preceding sentence shall include, without limitation, the right to research, develop, license and Commercialize products.

2.5. Orasense shall not be permitted to (a) encumber any of its rights under the Licenses or the Orasense Collaboration Intellectual Property without the prior written consent of Isis; (b) assign or sublicense any of its rights under the licenses for the Licensed Technologies and the Orasense Collaboration Intellectual Property without the prior written consent of Isis, which consent may be withheld in Isis' sole discretion. Any agreement between Orasense and any permitted third party for the development or exploitation of the Isis Intellectual Property shall be pursuant to a written sublicense agreement and require third party to maintain the confidentiality of all information concerning the Isis Intellectual Property (which confidentiality obligations shall be no less onerous than the confidentiality obligations of the Parties hereunder) and shall permit an assignment of rights by Orasense to Isis in accordance with the terms of this Agreement. Orasense shall remain responsible for all acts and omissions of any sub-licensee, as if they were acts and omissions by Orasense. Rights of permitted third party sublicensees in and to the Isis Intellectual Property shall survive the termination

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of the license and sublicense agreements granting said intellectual property rights to Orasense; and Orasense and Isis shall in good faith agree upon the form most advantageous to Isis in which the rights of the sublicensor under any such sublicenses are to be held (which form may include continuation of Orasense solely as the holder of such licenses or assignment of such rights to a third party or parties, including an assignment to Isis).

2.6. Orasense and its sublicensees, if any, shall be solely responsible for ensuring that the research, development, manufacture and Commercialization of the Products within each country of the Territory is strictly in accordance with all legal, regulatory requirements and applicable laws for each country of the Territory.

2.7. When Packaged, and to the extent permitted by law, a Label shall include an acknowledgement that the Product is made under license from Isis. Such acknowledgement shall take into consideration all regulatory requirements and applicable laws in each country of the Territory and Orasense's reasonable commercial requirements. Orasense shall wherever possible give due acknowledgement and recognition to Isis in all printed promotional and other material regarding the Product such as stating that the Product is under license from Isis and that the applicable Isis Intellectual Property has been applied to the Products. Orasense shall consult with and obtain the written approval of Isis as to the format and content of any promotional and other material insofar as it relates to a description of, or other reference to, the application of the Isis Intellectual Property, such approval not to be unreasonably withheld or delayed. The further consent of Isis shall not be required where the format and content of such materials is substantively similar as the materials previously furnished to and approved in writing by Isis.

2.8. Isis shall have the first option to manufacture the active ingredient of the Development Product for Orasense and meet its requirements, and Orasense shall agree to utilize Isis as its sole supplier, subject to the customary terms and conditions contained in a supply agreement to be executed by the parties at a price equal to Isis' actual manufacturing cost plus ten percent (10%). If, despite good faith negotiations, Isis and Orasense do not reach agreement on the terms of such manufacturing agreement within six (6) months from the Parties' commencement of discussion of such terms, then Orasense shall be free to offer a third party terms to manufacture the active ingredient of the Development Product in the Territory, which terms when taken as a whole, are more favorable to Orasense than the principal terms of the last written proposal offered to Orasense by Isis, or by Orasense to Isis, as the case may be.

### 3. **INTENTIONALLY DELETED**

### 4. **DEVELOPMENT OF PRODUCTS**

4.1. Orasense shall, or shall cause its sublicensees to, diligently pursue the research and development of the Elan Intellectual Property, Isis Intellectual Property and Orasense Collaboration Intellectual Property and shall use its, and shall cause its sublicensees to use their, commercially reasonable efforts to Commercialize a Product.

4.2. [\*\*\*].

### 5. **REGULATORY APPROVALS**

5.1. Orasense shall, or shall cause its sublicensees, at its or its sublicensees' sole cost and expense, to file and shall use its reasonable best efforts to prosecute to approval or cause its sublicensees to prosecute to approval, the Marketing Authorizations for the Products in the Territory. During any Marketing Authorization registration procedure, Orasense shall keep Isis promptly and fully advised of Orasense's registration activities, progress and procedures with respect to the Commercialization of any Product and the Oral Platform. Orasense shall, and shall cause its sublicensees to, inform Isis of any writings, dealings and other communications that Orasense and its sublicensees have with the FDA and any other Regulatory Authority with respect to the safety of the Product and the Oral Platform. The Parties shall collaborate in relation to obtaining any required approvals, including Regulatory Approval of any Regulatory Authority in each country in which Commercialization of the Product and the Oral Platform is sought for final Labeling.

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5.2. Subject to agreement to the contrary, any and all Marketing Authorizations filed hereunder for Products shall, to the extent owned by Orasense, remain the property of Orasense, provided that Orasense shall allow Isis access thereto to enable Isis to research, develop and Commercialize any product outside the Field. Orasense shall maintain or cause its sublicensees to maintain such Marketing Authorizations at its or their own cost and expense.

5.3. Orasense shall indemnify and hold harmless Isis, its agents and employees from and against all claims, damages, losses, liabilities and expenses to which Isis, its agents, and employees may become subject related to or arising out of Orasense's bad faith, negligence or intentional misconduct in connection with the filing or maintenance of the Marketing Authorizations.

## 6. FINANCIAL PROVISIONS

6.1 In consideration of the license to the Patents licensed to Orasense by Isis under the Isis License, Orasense shall pay to Isis, the following amounts:

6.1.1 *Development Product Fees and Royalties.* Payments to Isis with respect to services rendered in connection with the Development Product shall be paid as provided below and the gross profits of Orasense shall be distributed to Isis as set forth below.

6.1.2 *Development Work* — Research and development work performed during the Research Term pursuant to the Research Plan contracted by Orasense to Isis shall be payable by Orasense to Isis based on fully burdened actual costs at Isis's Full Time Equivalent Rate, with annual Cost of Living Increases.

6.1.3 *Royalty Payments* — After paying Elan its royalties pursuant to Section 6 of the Elan License Agreement, if any, Orasense [\*\*\*]

6.2 Payments pursuant to Clauses (a) and (b) above, if any, shall be made semi annually in arrears within [\*\*\*] days after the expiry of the applicable period. The method of payment shall be by wire transfer to an account specified by Isis and shall be nonrefundable to Orasense. Each payment made to Isis shall be accompanied by a true accounting of all Products sold by Orasense, its Affiliates and its permitted sublicensees, if any, during such quarter. Such accounting shall show, on a country-by-country and Product-by-Product basis, Net Sales, royalties received by Orasense (and the calculation thereof) and each calculation of royalties with respect thereto, including the calculation of all adjustments and currency conversions.

6.3 Orasense shall maintain and keep clear, detailed, complete, accurate and separate records for a period of [\*\*\*] following the completion of such records so: (i) as to enable any royalties which shall have accrued hereunder to be determined; and (ii) that any deductions made in arriving at the Net Sales can be determined.

6.4 All payments due hereunder shall be made in United States Dollars. Payments due on Net Sales of any Product, royalties received by Orasense with respect to any Product for each calendar quarter made in a currency other than United States Dollars shall first be calculated in the foreign currency and then converted to United States Dollars on the basis of the average exchange rate in effect for such quarter for the purchase of United States Dollars with such foreign currency quoted in the Wall Street Journal (or comparable publication if not quoted in the Wall Street Journal) with respect to the currency of the country of origin of such payment, determined by averaging the rates so quoted on each business day of such quarter.

6.5 If, at any time, legal restrictions in the Territory prevent the prompt payment when due of royalties or any portion thereof, the Parties shall meet to discuss suitable and reasonable alternative methods of reimbursing Isis the amount of such royalties. In the event that Orasense is prevented from making any payment under this Agreement by virtue of the statutes, laws, codes or government regulations of the country from which the payment is to be made, then such payments may be paid by

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depositing them in the currency in which they accrue to Isis's account in a bank acceptable to Isis in the country the currency of which is involved or as otherwise agreed by the Parties.

6.6 Isis and Orasense agree to co-operate in all respects necessary to take advantage of any double taxation agreements or similar agreements as may, from time to time, be available.

6.7 Any taxes payable by Isis on any payment made to Isis pursuant to this Agreement shall be for the account of Isis. If so required by applicable law, any payment made pursuant to this Agreement shall be made by Orasense after deduction of the appropriate withholding tax, in which event the Parties shall co-operate to obtain the appropriate tax clearance as soon as is practicable. On receipt of such clearance, Orasense shall forthwith procure that the amount so withheld is paid to Isis.

6.8 Orasense shall, not more than [\*\*\*] in each calendar year, permit Isis or its duly authorized representatives upon reasonable notice and at any reasonable time during normal business hours to have access to inspect and audit the accounts and records of Orasense and any other book, record, voucher, receipt or invoice relating to the calculation of the royalty payments on Net Sales submitted to Isis. Any such inspection of Orasense's records shall be at the expense of Isis, except that if any such inspection reveals a deficiency in the amount of the royalty actually paid to Isis hereunder in any calendar quarter [\*\*\*] or more of the amount of any royalty actually due to Isis hereunder, then the expense of such inspection shall be borne solely by Orasense. Any amount of deficiency shall be paid promptly to Isis by Orasense. If such inspection reveals a surplus in the amount of royalties actually paid to Isis by Orasense, Isis shall reimburse Orasense the surplus within fifteen (15) days after determination.

6.9 In the event of any unresolved dispute regarding any alleged deficiency or overpayment of royalty payments hereunder, the matter will be subject to resolution in accordance with Clause 24.9 of the Development Agreement, which is incorporated by reference and shall for such purposes survive termination of the Development Agreement.

## 7. CONFIDENTIAL INFORMATION

7.1. The Parties acknowledge that it may be necessary, from time to time, to disclose to each other confidential and proprietary information, including without limitation, Patents, inventions, works of authorship, trade secrets, specifications, designs, data, Know-How and other information relating to the Field, the Products, Elan Intellectual Property, Isis Intellectual Property and Orasense Intellectual Property, as the case may be, processes, services and business of the disclosing Party. The foregoing shall be referred to collectively as "Confidential Information". Any Confidential Information revealed by a Party to another Party shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's obligations under this Agreement and the Development Agreement and for no other purpose.

7.2. Each Party agrees to disclose Confidential Information of another Party only to those employees, representatives and agents requiring knowledge thereof in connection with their duties directly related to the fulfilling of the Party's obligations under this Agreement. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information. Each Party agrees that it will exercise the same degree of care, but in no event less than a reasonable degree, and protection to preserve the proprietary and confidential nature of the Confidential Information disclosed by a Party, as the receiving Party would exercise to preserve its own



proprietary and confidential information. Each Party agrees that it will, upon request of a Party, return all documents and any copies thereof containing Confidential Information belonging to or disclosed by, such Party.

7.3. Notwithstanding the above, each Party may use or disclose Confidential Information disclosed to it by another Party to the extent such use or disclosure is reasonably necessary in filing or

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prosecuting patent applications, prosecuting or defending litigation, complying with patent applications, complying with applicable governmental regulations or otherwise submitting information to tax or other governmental authorities, conducting clinical trials, or making a permitted sub-license or otherwise exercising its rights hereunder, provided that if a Party is required to make any such disclosure of the other Party's Confidential Information, other than pursuant to a confidentiality agreement, such Party shall inform the recipient of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information.

7.4. Any breach of this Clause 7 by any of the Persons informed by one of the Parties is considered a breach by the Party itself.

7.5. Confidential Information shall not be deemed to include:

7.5.1. information that is generally available to the public;

7.5.2. information which is made public by the disclosing Party;

7.5.3. information which is independently developed by a Party as evidenced by such Party's written records, without the aid, application or use of the disclosing Party's Confidential Information;

7.5.4. information that is published or otherwise becomes part of the public domain without any disclosure by a Party, or on the part of a Party's directors, officers, agents, representatives or employees;

7.5.5. information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis;

7.5.6. information which the receiving Party is required to disclose pursuant to:

7.5.6.1. a valid order of a court or other governmental body or any political subdivision thereof or otherwise required by law; or

7.5.6.2. any other requirement of law;

provided that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or other appropriate remedy concerning any such disclosure. The receiving Party shall fully cooperate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required;

7.5.7. information which was already in the possession of the receiving Party at the time of receiving such information, as evidenced by its written records, provided such information was not previously provided to the receiving Party from a source which was under an obligation to keep such information confidential; or

7.5.8. information that is the subject of a written permission to disclose, without restriction or limitation, by the disclosing Party.

7.6. The provisions relating to confidentiality in this Clause 7 shall remain in effect during the term of this Agreement, and for a period of [\*\*\*] following the expiration or earlier termination of this Agreement but shall not apply to any information which a Party is required to file or otherwise disclose in accordance with requirements which are legally binding on it.

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7.7. The Parties agree that the obligations of this Clause 7 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party expressly agrees that monetary damages would be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein. Accordingly, the Parties agree and acknowledge that any such violation or threatened violation will cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, any Party shall be entitled to obtain injunctive relief against the threatened breach of the provisions of this Clause 7, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

7.8. Each of the Parties shall be entitled to provide a copy of this Agreement (and any subsequent amendments hereto) and the Development Agreement to a potential third party purchaser in connection with the sale of such Party's business or assets, including without limitation, in the case of Elan, the sale of the Elan Intellectual Property; provided that the relevant third party purchaser or assignee has entered into a confidentiality agreement on terms no less protective than the terms of this Clause 7.

## 8. WARRANTIES AND INDEMNITIES

8.1 Isis represents and warrants to Orasense as of the Original Effective Date that:

8.1.1 Isis is a corporation duly organized under the laws of its jurisdiction of organization and has all the requisite corporate power and authority to own and lease its respective properties, to carry on its respective business as presently conducted and as proposed to be conducted and to carry out the

transactions contemplated hereby;

8.1.2 Isis has full corporate power and authority to enter into this Agreement and to perform its obligations hereunder, which have been duly authorized by all requisite corporate action of Isis. This Agreement is the valid and binding obligation of Isis, enforceable against it in accordance with its terms, except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and by general equity principles and limitations on the availability of equitable relief, including specific performance;

8.1.3 the execution, delivery and performance by Isis of this Agreement will not: (i) violate any provision of applicable law, statute, rule or regulation known by and applicable to Isis or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to Isis or any of its properties or assets; or (ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under the charter or organizational documents of Isis to which Isis is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have an adverse material effect on the business, assets, liabilities (contingent or otherwise), operations, condition (financial or otherwise), or prospects of Isis;

8.1.4 to Isis's best knowledge, except as set forth on Schedule 3 hereto, (i) Isis has the right to grant the Isis License, (ii) there are no agreements between Isis and any third parties that conflict with the Isis License which would have a material adverse effect on the ability of Orasense to conduct its business as presently proposed to be conducted, (iii) Isis is the owner or licensee of all rights, title and interest in the Isis Intellectual Property; and (v) [\*\*\*]

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8.2 Orasense represents and warrants to Isis as of the Original Effective Date that:

8.2.1 Orasense is duly and validly existing in good standing in the jurisdiction of its incorporation and each other jurisdiction in which the conduct of its business requires such qualification (except where such failure to so qualify shall not have a material adverse affect on the business and assets of Orasense), and Orasense is in compliance with all applicable laws, rules, regulations or orders relating to its business and assets;

8.2.2 Orasense has full corporate authority to execute and deliver this Agreement and to consummate the transactions contemplated hereby; this Agreement has been duly executed and delivered and constitutes the legal and valid obligations of Orasense and is enforceable against Orasense in accordance with its terms; and the execution, delivery and performance of this Agreement and the transactions contemplated hereby will not violate or result in a default under or creation of lien or encumbrance under Orasense's certificate of incorporation, by-laws or other organizational documents, any material agreement or instrument binding upon or affecting Orasense, or its properties or assets or any applicable laws, rules, regulations or orders affecting Orasense or its properties or assets;

8.2.3 Orasense is not in default of its charter or by-laws, any applicable laws or regulations or any material contract or agreement binding upon or affecting it or its properties or assets and the execution, delivery and performance of this Agreement and the transactions contemplated hereby will not result in any such violation;

8.2.4 Orasense represents and warrants to Elan that the execution of this Agreement by Orasense and the full performance and enjoyment of the rights of Orasense under this Agreement will not breach the terms and conditions of any license, contract, understanding or agreement, whether express, implied, written or oral between Orasense and any third party;

8.2.5 Orasense represents and warrants to and covenants with Isis that it has the sole, exclusive and unencumbered right to grant the licenses and rights herein granted to Isis and that it has not granted and will not grant any option, license, right or interest in or to the Isis Intellectual Property, the Orasense Collaboration Intellectual Property, or other property to any third party which would conflict with the rights granted by this Agreement;

8.2.6 the Products shall be developed, manufactured, transported, stored, handled, Packaged, marketed, promoted, distributed, offered for sale, sold and otherwise Commercialized in accordance with all regulations and requirements of the FDA and foreign governmental authorities having jurisdiction in such country or countries in the Territory including, without limitation, cGCP, cGLP, cGMP regulations.

8.2.7 the Products shall not be adulterated or misbranded as defined by the Federal Food, Drug and Cosmetic Act (or applicable foreign law) and shall not be a product which would violate any section of such Act if introduced in interstate commerce;

8.2.8 it is fully cognizant of all applicable statutes, ordinances and regulations of the United States of America and countries in the Territory with respect to the manufacture of the Products including, but not limited to, the U.S. Federal Food, Drug and Cosmetic Act and regulations thereunder and similar statutes in countries outside of the United States. Orasense shall manufacture or procure the manufacture of the Products in conformity with the Marketing Authorizations and in a manner which fully complies with all United States of America and foreign statutes, ordinances, regulations and practices.

8.3 In addition to any other indemnifications provided for herein, Isis shall indemnify and hold harmless Orasense and their respective employees, agents, partners, officers and directors from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses)

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incurred or sustained by Orasense arising out of or in connection with any (a) breach of any representation, covenant, warranty or obligation by Isis hereunder, or (b) any act or omission on the part of Isis or any of its agents or employees in the performance of this Agreement.

8.4 In addition to any other indemnifications provided for herein, Orasense shall indemnify and hold harmless Isis and its employees, agents, partners, officers and directors (each an "Indemnified Party") from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by an Indemnified Party arising out of or in connection with any (a) breach of any representation, covenant, warranty or obligation by

Orasense or its sublicensees hereunder, or (b) any act or omission on the part of Orasense in connection with the research, development, manufacture and/or Commercialization of any Product hereunder, including without limitation, with respect to the conduct of any clinical trials and death or injury to any person.

8.5 Orasense shall each obtain prior to conducting any clinical trial in respect of the Product appropriate comprehensive general liability insurance and/or other insurance coverage (the "Policies"), and shall each maintain such Policies during such clinical trials and for a period of five years thereafter. Orasense shall furnish to Isis copies of all Policies which each holds in respect of such clinical trials.

8.6 Any Party seeking an indemnity hereunder shall:

8.6.1 fully and promptly notify the other Party of any claim or proceeding, or threatened claim or proceeding;

8.6.2 permit the indemnifying Party to take full care and control of such claim or proceeding;

8.6.3 cooperate in the investigation and defense of such claim or proceeding;

8.6.4 not compromise or otherwise settle any such claim or proceeding without the prior written consent of the other Party, which consent shall not be unreasonably withheld, conditioned or delayed; and

8.6.5 take all reasonable steps to mitigate any loss or liability in respect of any such claim or proceeding.

**8.7 NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, ISIS, ELAN AND ORASENSE SHALL NOT BE LIABLE TO THE OTHER PARTIES, BY REASON OF ANY REPRESENTATION OR WARRANTY, CONDITION OR OTHER TERM OR ANY DUTY OF COMMON LAW, OR UNDER THE EXPRESS TERMS OF THIS AGREEMENT, FOR ANY CONSEQUENTIAL, SPECIAL OR INCIDENTAL LOSS OR DAMAGE (WHETHER FOR LOSS OF PROFIT OR OTHERWISE) AND WHETHER OCCASIONED BY THE APPLICABLE PARTY'S NEGLIGENCE OR OF ITS EMPLOYEES OR AGENTS OR OTHERWISE.**

**8.8 EXCEPT AS SET FORTH IN THIS CLAUSE 8, ISIS IS GRANTING THE ISIS LICENSE HEREUNDER ON AN "AS IS" BASIS WITHOUT RECOURSE, REPRESENTATION OR WARRANTY WHETHER EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR INFRINGEMENT OF THIRD PARTY RIGHTS, AND ALL SUCH WARRANTIES ARE EXPRESSLY DISCLAIMED.**

## 9 INTELLECTUAL PROPERTY OWNERSHIP RIGHTS

9.1 Title and all other ownership rights, including patent rights, relating to the Isis Intellectual Property shall belong to Isis.

9.2 Each Party shall own the legal and equitable title to any invention invented by such Party that is not Orasense Intellectual Property.

9.3 Orasense shall permanently mark or otherwise use reasonable efforts to cause any third party to permanently mark all Products and/or the Packaging therefor with such license or patent notices to

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comply with the applicable laws of each country of sale of the Territory or otherwise to generally communicate the existence of any of Patents under the Isis Intellectual Property for the countries of the Territory and in such manner as Isis may reasonably request in writing following receipt of written notice by Orasense of its intent to Commercialize a Product.

9.4 Isis, at its expense, shall (i) secure the grant of any material patent applications in the Territory to the Isis Delivery Technology that relate to the Field and the Isis Development Candidate Technology; (ii) defend all such applications against third party oppositions; and (iii) maintain in force any material issued letters patent within the Isis Delivery Technology that relate to the Field and the Isis Development Candidate Patents. Isis shall have the right in its discretion to control such filing, prosecution, defense and maintenance provided that Orasense and Elan at their request shall be provided with copies of all documents relating to such filing, prosecution, defense and maintenance in sufficient time to review such documents and comment thereon prior to filing.

9.5 In the event that Isis informs Orasense and Elan that it does not intend to file patent applications on patentable inventions and discoveries within the Isis Intellectual Property that relate to the Field in one or more countries in the Territory or fails to file such an application within a reasonable period of time, Orasense shall have the option at its expense to file and prosecute such patent application(s) in the joint names of Orasense and Isis. Upon written request from Orasense, Isis shall execute all documents, forms and declarations and to do all things as shall be reasonably necessary to enable Orasense to exercise such option.

9.6 Orasense, Isis and Elan shall promptly inform each other in writing of any alleged infringement of any patents within the Patents within the Isis Intellectual Property and the Orasense Intellectual Property or any alleged misappropriation of trade secrets within the Isis Intellectual Property or the Orasense Intellectual Property by a third party of which it becomes aware and provide the others with any available evidence of such infringement or misappropriation insofar as such infringements or misappropriation relate solely to the Field.

9.7 Orasense shall have the right to prosecute at its own expense and for its own benefit any infringements of the Patents within the Isis Intellectual Property or misappropriation of the Isis Intellectual Property, insofar as such infringements or misappropriation relate solely to the Field. In the event that Orasense takes such action, Orasense shall do so at its own cost and expense. At Orasense's request, Isis shall cooperate with such action. Any recovery in relation to such infringement proceeding shall belong to Orasense. Should Orasense decide not to pursue such infringers, within a reasonable period but in any event within [\*\*\*] after receiving written notice of such alleged infringement or misappropriation Isis may in its discretion initiate such proceedings in its own name, at its expense and for its own benefit, and at Isis's request, Orasense shall cooperate with such action. Alternatively, Orasense and Isis may agree to institute such proceedings in their joint names and shall reach agreement as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party. If the infringement of the Patents within the Isis Intellectual Property affects both the Field as well as other products being developed or commercialized by Isis or its commercial partners outside the Field, Orasense and Isis shall endeavor to agree as to the manner in which the proceedings should be instituted and as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party.

10.1 *Licenses to Orasense.* Subject to the Non-Competition provisions in Clause 11 hereof, Orasense hereby grants to Isis for the Term:

10.1.1 an exclusive, royalty free and sublicensable license to practice the Orasense Collaboration Intellectual Property in the Field in the Territory;

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10.1.2 an exclusive, royalty free and sublicensable license to practice the Orasense Post-Collaboration Intellectual Property, and

10.1.3 a [\*\*\*], royalty free and sublicensable license with Elan to practice Orasense Collaboration Intellectual Property [\*\*\*] in the Territory.

## 11 **NON-COMPETITION**

During [\*\*\*], Isis shall not develop or Commercialize, or assist in the development or Commercialization of an [\*\*\*], except (a) for or on behalf of Orasense, or (b) with the prior written, unanimous consent of the Management Committee. During the Research Term and provided that Orasense is maintaining an active program for the development and Commercialization of the Development Candidate in the Field, Isis shall not develop or Commercialize or assist in the development for Commercialization [\*\*\*] Nothing contained herein shall be construed as (i) limiting the activities of an existing third party licensee of Isis from developing Oligonucleotide Drugs utilizing Isis Delivery Technology to the extent such rights have been previously granted by Isis, provided Isis does not provide any active support to any such activities in excess of its existing contractual obligations or (ii) prohibiting Isis from licensing Isis Delivery Technology to an Independent Third Party or limiting the activities of any such future Independent Third Party licensee of Isis from developing [\*\*\*] utilizing Isis Delivery Technology [\*\*\*].

## 12 **TERM AND TERMINATION OF AGREEMENT**

12.1 The term of this Agreement and the term of the Isis License granted hereunder with respect to a Product utilizing or based on the Licensed Technologies shall commence as of the Effective Date and continue, on a Product-by-Product basis and country by country basis, for the life of the Patent rights upon which such Product is based on or utilizes in such country (the "Term"); provided, however, that all royalty and fee obligations contained herein shall survive for the greater of (i) the Term or (ii) [\*\*\*] years from the first commercial sale of such Product.

12.2 Nothing contained herein shall obligate or restrict any party from utilizing public, non-proprietary information which is not subject to the protection of applicable patent laws.

12.3 If any Party breaches any material provision of this Agreement and if such breach is (i) not capable of being cured or (ii) is capable of being cured but is not corrected within [\*\*\*] after the non-breaching Party gives written notice of the breach to the breaching Party, the non-breaching Party may terminate this Agreement immediately by giving notice of the termination to the breaching Party, effective on the date of the notice, *provided, however*, that (x) if any such curable breach is not capable of being cured within [\*\*\*] period, so long as the breaching Party takes substantial steps to cure the breach promptly after receiving notice of the breach from the non-breaching party and thereafter diligently prosecutes the cure to completion as soon as is practicable, the non-breaching Party may not terminate this Agreement so long as the breaching party is acting in good faith to rectify such breach; provided, however, that, the completion of cure may not, in any event, exceed, [\*\*\*] months from the date of receipt of notice by the breaching Party of its breach hereunder, or (y) the default involves a good faith dispute regarding the amount of any required payment, provided any undisputed amount is timely paid, such default shall be stayed and the remainder may be withheld for a reasonable period of time not to [\*\*\*] days during which a good faith resolution of the amount owed is being pursued.

12.4 In the event that the Isis License Agreement shall be terminated, at the sole option of Elan and upon written notice to Isis and Orasense, the Elan License shall be immediately terminated.

12.5 In the event of an Failure to Fund, the Isis Development Candidate License will automatically terminate and all rights in the Isis Development Candidate Technology will revert back to Isis.

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12.6 Upon the occurrence of an Event of Bankruptcy with respect to Orasense, Isis or Elan, the other Party may, upon written notice to Isis and the Party with respect to which such Event of Bankruptcy has occurred, immediately terminate the Elan License. As used in this Clause 12.5, the term "Event of Bankruptcy" relating to either Orasense or Elan shall mean:

12.6.1 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of either Party of it or over all or a substantial part of its assets under the law of any applicable jurisdiction, including without limit, Bermuda, the United States of America or Ireland; or

12.6.2 an application or petition for bankruptcy, corporate re-organization, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limit, Bermuda, the United States of America or Ireland (other than as part of a bona fide restructuring or reorganization), is filed, and is not discharged within forty-five (45) days, or if either Party applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of either Party are for any reason seized, confiscated or condemned.

12.7 Upon exercise of those rights of termination as specified in Clause 12.1 to Clause 12.5 inclusive or elsewhere within this Agreement, this Agreement shall, subject to the other provisions of this Agreement, automatically terminate forthwith and be of no further legal force or effect.

12.8 Upon expiration or termination of the Agreement:

12.8.1 any sums that were due from Orasense to Isis under Clause 6, including without limitation on Net Sales, in the Territory or in such particular country or countries in the Territory (as the case may be) prior to the expiration or termination of this Agreement as set forth herein shall be paid in full

within sixty (60) days after the expiration or termination of this Agreement for the Territory or for such particular country or countries in the Territory (as the case may be);

12.8.2 any provisions clearly meant to survive termination or expiration of this Agreement, including without limitation Clause 7, shall remain in full force and effect;

12.8.3 all representations, warranties and indemnities shall insofar as are appropriate remain in full force and effect;

12.8.4 the rights of inspection and audit set out in Clause 12.7 shall continue in force for a period of [\*\*\*];

12.8.5 termination of this Agreement for any reason shall not release any Party hereto from any liability which, at the time of such termination, has already accrued to the other Party or which is attributable to a period prior to such termination nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement;

12.8.6 the Isis Intellectual Property and all rights, licenses and sublicenses granted by Isis in and pursuant to this Agreement shall cease for the Territory or for such particular country or countries in the Territory (as the case may be) and shall immediately revert to Isis. Following such expiration or termination, Orasense may not thereafter use in the Territory or in such particular country or countries in the Territory (as the case may be) (a) any valid and unexpired Patents in the Isis Intellectual Property and/or (b) any Isis Intellectual Property that remains confidential or otherwise proprietary to Isis. All rights to Orasense Intellectual Property will be transferred to and owned by Orasense. Rights of permitted Independent Third Party sublicensees in and to the Isis Intellectual Property shall survive the termination of the license and sublicense agreements granting said intellectual property rights to Orasense; and Orasense, Isis and Elan shall in good

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faith agree upon the form most advantageous to Elan and Isis in which the rights of the sublicensor under any such sublicenses are to be held (which form may include continuation of Orasense solely as the holder of such licenses or assignment of such rights to a third party or parties, including an assignment to both Isis and Elan). Any sublicense agreement between Orasense and such permitted sublicensee shall permit an assignment of rights by Orasense to Isis and shall contain additional reasonable confidentiality protections which an assignee shall reasonably require. Upon any such assignment, Elan and Isis shall enter into good faith negotiations with respect to additional reasonable confidentiality protections which either party shall reasonably require.

### 13 FORCE MAJEURE

13.1 Neither Party to this Agreement shall be liable for delay in the performance of any of its obligations hereunder if such delay results from causes beyond its reasonable control, including, without limitation, acts of God, fires, strikes, acts of war, or intervention of a government authority, non availability of raw materials, but any such delay or failure shall be remedied by such Party as soon as practicable; provided, however, that neither party hereunder shall be excused for delay in the performance of any of its payment obligations hereunder.

### 14 SETTLEMENT OF DISPUTES; GOVERNING LAW

14.1 Any dispute between the Parties arising out of or relating to this Agreement will be subject to resolution in accordance with Clause 24.9 of the Development Agreement, which is incorporated by reference and shall for such purposes survive termination of the Development Agreement.

14.2 This Agreement is construed under and ruled by the laws of the State of New York, without regard to the conflict of law principles.

### 15 ASSIGNMENT

This Agreement may not be assigned by either Party without the prior written consent of the other, which consent shall not be unreasonably withheld, conditioned or delayed, save that (i) either Party may assign this Agreement to its Affiliate without such consent, provided that such assignment does not have any adverse tax consequences on the other Party, and (ii) Isis may assign its rights and obligations hereunder in connection with a sale of its business or sale of any of the Isis Intellectual Property licensed hereunder, whether by merger, sale of stock, sale of assets or otherwise. Isis, Elan and Orasense will discuss any assignment by either Party to an Affiliate prior to its implementation in order to avoid or reduce any additional tax liability to the other Party resulting solely from different tax law provisions applying after such assignment to an Affiliate. For the purpose hereof, an additional tax liability shall be deemed to have occurred if either Party would be subject to a higher net tax on payments made hereunder after taking into account any applicable tax treaty and available tax credits than such Party was subject to before the proposed assignment. Notwithstanding any assignment hereof to an Affiliate, each Party will remain fully liable hereunder.

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### 16 NOTICES

16.1 Any notice to be given under this Agreement shall be sent in writing in English by registered airmail or telefaxed to the following addresses:

If to Orasense at:	Orasense Ltd. c/o Isis Pharmaceuticals, Inc. 2292 Faraday Avenue Carlsbad, California 92008 Attention: Ms. Lynne Parshall Telephone: (760) 603-2460 Telefax: (760) 931-9639
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If to Isis to:	Isis Pharmaceuticals, Inc.
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2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: Ms Lynne Parshall  
Telephone: (760) 603-2460  
Telefax: (760) 931-9639

with a copy to: Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: Grantland E. Bryce  
Telephone: 760-603-2707  
Fax: 760-268-4922

If to Elan at: Elan Corporation, plc  
C/o Elan International Services, Ltd.  
102 St. James Court  
Flatts,  
Smiths FL04  
Bermuda  
Attention: Secretary  
Telephone: 441 292 9169  
Fax: 441 292 2224

or to such other address(es) and telefax numbers as may from time to time be notified by either Party to the other hereunder.

16.2 All notices and other communications given to any Party hereto in accordance with the provisions of this Agreement will be deemed to have been given on the date of receipt if delivered by hand or overnight courier service or sent by confirmed teletype to such Party as provided in this Clause or in accordance with the latest unrevoked direction from such Party given in accordance with this Clause 16.

## 17 MISCELLANEOUS CLAUSES

17.1 No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any other breach or failure to perform or of any other right arising under this Agreement.

17.2 If any provision in this Agreement is agreed by the Parties to be, or is deemed to be, or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto,

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17.2.1 such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable or, if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of such agreement or such earlier date as the Parties may agree; and

17.2.2 the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

17.3 The Parties shall use their respective reasonable endeavors to ensure that the Parties and any necessary third party shall execute and perform all such further deeds, documents, assurances, acts and things as any of the Parties hereto may reasonably require by notice in writing to the other Party or such third party to carry the provisions of this Agreement.

17.4 This Agreement shall be binding upon and inure to the benefit of the Parties hereto, their successors and permitted assigns and sublicensees.

17.5 No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between the Parties unless specifically referred to, and solely to the extent provided, in any such other agreement. In the event of a conflict between the provisions of this Agreement and the provisions of the Development Agreement, the terms of this Agreement shall prevail.

17.6 No amendment, modification or addition hereto shall be effective or binding on either Party unless set forth in writing and executed by a duly authorized representative of each Party. Amendments hereto shall be subject to the prior approval of Elan, which approval shall not be unreasonably withheld or delayed.

17.7 This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

17.8 Each of the Parties undertakes to do all things reasonably within its power which are necessary or desirable to give effect to the spirit and intent of this Agreement.

17.9 Each of the Parties hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty save as expressly set out herein or in any document referred to herein.

17.10 Nothing contained in this Agreement is intended or is to be construed to constitute Elan, Isis and Orasense as partners, or Isis as an employee of Orasense and Elan, or Orasense and Elan as an employee of Isis. Neither Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of the other Party or to bind the other Party to any contract, agreement or undertaking with any third party.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the date first set forth above.

**ELAN CORPORATION, PLC**

**ISIS PHARMACEUTICAL, INC.**

By: /s/ KEVIN INSLEY

By: /s/ B. LYNNE PARSHALL

Kevin Insley

B. Lynne Parshall

Name

Name

Title Authorized Signatory

Title Executive VP, CFO, Director

Date

Date October 24, 2002

**ORASENSE, LTD.**

By: /s/ E.C. (NED) JACKSON

E.C. (Ned) Jackson

Name

Title

Date

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**EXHIBIT A**

**Description of Development Candidate**

[\*\*\*]

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**SCHEDULE 1A**

**Isis Intellectual Property  
(Isis Development Candidate Technology)**

[\*\*\*]

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**SCHEDULE 2**

**ORASENSE COLLABORATION INTELLECTUAL PROPERTY**

[\*\*\*]

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**SCHEDULE 3**

**Isis Exceptions and Disclosures**

[\*\*\*]

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## QuickLinks

[AMENDED AND RESTATED LICENSE AGREEMENT BY AND BETWEEN ORASENSE LTD A Bermuda Limited Company, ISIS PHARMACEUTICALS, INC A Delaware Corporation AND ELAN CORPORATION, PLC A Public Irish Company October 24, 2002](#)



**Elan License Agreement  
Execution Copy (V9)  
24 October 2002**

**AMENDED AND RESTATED  
LICENSE AGREEMENT**

**BY AND BETWEEN**

**ORASENSE LTD  
A Bermuda Limited Company**

**ISIS PHARMACEUTICALS, INC  
A Delaware Corporation**

**AND**

**ELAN CORPORATION, PLC  
A Public Irish Company**

**October 24, 2002**

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**RECITALS:**

A. Contemporaneously herewith, Elan, EIS, Orasense and Isis (capitalized terms used herein are defined below) are entering into the Development Agreement for the purpose of amending, restating and recording the terms and conditions of a joint venture and of regulating their relationship with each other and certain aspects of the affairs of and their dealings with Orasense.

B. Elan is beneficially entitled to the use of certain know-how and certain patents that have been granted or are pending in relation to the development and production of various drug delivery technologies and drug products.

C. Orasense desires to enter into this Agreement with Elan so as to permit Orasense to utilize the Elan Intellectual Property in the research, development, manufacture, distribution and sale of Products in the Field and in the Territory.

D. Orasense and Elan entered into that certain License Agreement (the "Original License Agreement") dated April 20, 1999 (the "Original Effective Date"). The Parties now wish to amend, restate and supercede the Original License Agreement with this Agreement.

**NOW THEREFORE, IT IS HEREBY AGREED AS FOLLOWS:**

**1. DEFINITIONS; INTERPRETATION**

A. *Definitions.* In this Agreement, the following definitions shall apply:

1.1. "Affiliate" shall mean, with respect to Isis or Elan, any corporation or entity other than Orasense (and entities controlled by it) controlling, controlled or under the common control of Isis or Elan, as the case may be, and, with respect to Orasense, any corporation or entity under control of Orasense, but excluding, in the case of Elan, an Elan JV. A corporation or non-corporate entity shall be regarded as in control of another corporation if it owns or directly or indirectly controls at least fifty percent (50%) of the voting stock of the other corporation or (a) in the absence of the ownership of at least fifty percent (50%) of the voting stock of a corporation or (b) in the case of a non-corporate entity, the power to direct or cause the direction of the management and policies of such corporation or non-corporate entity, as applicable.

1.2. "Agreement" shall mean this agreement (which expression shall be deemed to include the Recitals and the Schedules hereto);

1.3. "cGCP", "cGLP" and "cGMP" shall mean current Good Clinical Practices, current Good Laboratory Practices and current Good Manufacturing Practices respectively;

1.4. "Commercialization" shall mean the manufacture, promotion, distribution, marketing and sale of the Products;

1.5. "Control" shall mean the ability of a Party to grant a license or sublicense as contemplated herein without having to obtain the prior consent of any third party or having to amend any agreement between such Party and a third party;

1.6. "Cost of Living Increase" shall mean, with respect to any year of the Term, any increase in the Consumer Price Index published by the Bureau of Labor Statistics of the United States Department of Labor, All Urban Consumers, United States City Average, All Items (1982-84=100);

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1.7. "Development Agreement" shall mean the Amended and Restated Joint Development and Operating Agreement of even date entered into among Elan, Isis, EIS and Orasense;

1.8. "Development Candidate" shall mean ISIS 104838, [\*\*\*] of TNF-a, as more specifically detailed in Exhibit A hereto;

1.9. "Development Product" shall mean any product containing as an active ingredient the Development Candidate formulated using the Oral Platform for humans;

1.10. "Effective Date" shall mean the date of execution and delivery of this Agreement;

1.11. "EIS" shall mean Elan International Services, Ltd., a Bermuda limited company;

1.12. "Elan" shall mean Elan Corporation, plc, a public limited company incorporated under the laws of Ireland, its, successors and permitted assigns;

1.13. "Elan Intellectual Property" shall mean (a) the Patents set forth in Schedule 1 hereof; and (b) Know-How Controlled by Elan that is necessary to practice within the Field. For the avoidance of doubt, Elan Intellectual Property shall not [\*\*\*]

1.14. "Elan JV" shall mean an entity that Elan and a third party (i) establish or have established; (ii) take shareholdings in or have a right to take shareholdings in; and (iii) grant certain licenses in and to certain intellectual property rights for the purpose of implementing a strategic alliance;

1.15. "Elan License" shall have the meaning set forth in Clause 2.1;

1.16. "Elan License Agreement" shall mean this Agreement;

1.17. "FDA" shall mean the United States Food and Drug Administration or any successors or agency the approval of which is necessary to market a product in the United States of America;

- 1.18. "Field" shall mean the research, development and Commercialization of the Oral Platform for use with Oligonucleotide Drugs;
- 1.19. "Full Time Equivalent Rate" shall mean, for services proposed to be rendered by Elan, [\*\*\*]
- 1.20. "Independent Third Party" shall mean any person other than Orasense, Elan, Isis or any of their respective Affiliates;
- 1.21. "Isis" shall mean Isis Pharmaceuticals, Inc., a Delaware corporation, its successors and permitted assigns;
- 1.22. "Isis Delivery Technology" shall have the meaning set forth in the Isis License Agreement;
- 1.23. "Isis Development Candidate Technology" shall have the meaning set forth in the Isis License Agreement;
- 1.24. "Isis Intellectual Property" shall have the meaning set forth in the Isis License Agreement.
- 1.25. "Isis License" shall have the meaning set forth in the Isis License Agreement
- 1.26. "Isis License Agreement" shall mean that certain amended and restated license agreement between Isis, Orasense and Elan of even date herewith;
- 1.27. "Know-How" shall mean any and all rights to any discovery, invention (whether or not patentable), know-how, substances, data, techniques, processes, systems, formulations and designs, which is not generally known to the public;
- 1.28. "Label", "Labeled" or "Labeling" shall mean all labels and other written, printed or graphic matter upon (i) the Product or any container or wrapper utilized with the Product, or (ii) any written material accompanying the Product, including, without limitation, package inserts;

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- 1.29. "Licensed Technologies" shall mean the Elan Intellectual Property and the Isis Intellectual Property;
- 1.30. "Licenses" shall mean the Elan License and the Isis License;
- 1.31. "Lien" shall mean any and all liens, security interests, restrictions, claims, encumbrances or rights of third parties of every kind and nature;
- 1.32. "Management Committee" shall have the meaning given to such term in the Development Agreement;
- 1.33. "Marketing Authorization" shall mean any and all consents or other authorizations or approvals required from a Regulatory Authority or other governmental authority to Commercialize a pharmaceutical product in a country in the Territory;
- 1.34. "Net Sales" shall mean, [\*\*\*]
- 1.35. "Oligonucleotide Drug" shall mean any single stranded [\*\*\*] at physiological pH oligonucleotide including those [\*\*\*] used as a human therapeutic and/or prophylactic compound containing between [\*\*\*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [\*\*\*]. For purposes of this agreement, Oligonucleotide Drug shall specifically exclude oligonucleotides used [\*\*\*] oligonucleotides used as [\*\*\*] an oligonucleotide, oligonucleotides used as [\*\*\*] or oligonucleotides used as [\*\*\*];
- 1.36. "Oral Platform" shall mean formulation and excipient systems and technologies [\*\*\*] which use [\*\*\*] to develop dosage forms of drugs and deliver said dosage forms to the [\*\*\*] to achieve a local or systemic therapeutic effect;
- 1.37. "Orasense" shall mean Orasense, Ltd., a Bermuda limited company, its successors and permitted assigns;
- 1.38. "Orasense Collaboration Intellectual Property" shall mean (a) Know-How Controlled by Orasense through the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made on or before the end of the Research Term, and/or (c) inventions and Patents issued thereon developed by Orasense, Isis and/or Elan on behalf of Orasense (or any third party under contract with Orasense, Isis and/or Elan) or otherwise under the Original Research Plan or the Research Plan. Schedule 2 to this Agreement shall contain, by way of illustration but not limitation, examples of Orasense Collaboration Intellectual Property. At the end of the Research Term, the Parties shall amend Schedule 2, as may be necessary. For the avoidance of doubt, Orasense Collaboration Intellectual Property does not include any Patents and Know-How Controlled by Elan or Isis, as the case may be.
- 1.39. "Orasense Intellectual Property" shall mean Orasense Collaboration Intellectual Property and Orasense Post Collaboration Intellectual Property;
- 1.40. "Orasense Post-Collaboration Intellectual Property" shall mean (a) Know-How Controlled by Orasense after the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made after the end of the Research Term, and/or (c) inventions and Patents issued thereon made by Isis on Orasense's behalf after a Failure to Fund. For the avoidance of doubt, Orasense Post-Collaboration Intellectual Property does not include any Patents and Know-How Controlled by Elan or Isis, as the case may be;
- 1.41. "Original Research Plan" means the Research and Development Program under that certain Subscription, Joint Development and Operating Agreement between Elan, EIS, Isis and Orasense dated April 20, 1999;

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- 1.42. "Package", "Packaged" and "Packaging" shall mean all primary and secondary packaging components, including, without limitation, cartons, partitions, shippers or any other like matter used in packaging the Product;

1.43. "Parties" shall mean Elan, Isis and Orasense and "Party" shall mean Elan, Isis or Orasense;

1.44. "Patents" shall mean any and all patents and patent applications under the Control of a Party hereto. Patents shall also include all extensions, continuations, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts of such patents and patent applications and any patents issuing thereon and extensions of any patents licensed hereunder;

1.45. "Person" shall mean an individual, partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture, or other entity of whatever nature;

1.46. "Primary Royalty Product" shall mean [\*\*\*]

1.47. "Product" shall mean any drug under development or developed by or on behalf of Orasense made or formulated using the Isis Delivery Technology, the Elan Intellectual Property and/or the Orasense Intellectual Property for administration to humans;

1.48. "Regulatory Application" shall mean a regulatory application or other application (including any supplements or amendments thereto) required to be filed or filed with a Regulatory Authority in a country in connection with the Commercialization of a pharmaceutical product in such country.

1.49. "Regulatory Authority" shall mean any regulatory authority outside the United States of America, the approval of which is necessary to market a Product;

1.50. "Research Plan" shall have the meaning set forth in the Development Agreement;

1.51. "Research Term" shall mean the period commencing on [\*\*\*] and continuing through [\*\*\*], and any extension thereto by the mutual agreement of Isis and Elan;

1.52. "Royalty Payment" shall mean a royalty payment made pursuant to Section 6.1.1(b);

1.53. "Royalty Product" means a Primary Royalty Product and/or a Secondary Royalty Product, as the case may be.

1.54. "Secondary Royalty Product" shall mean [\*\*\*]

1.55. "Term" shall have the meaning set forth in Clause 12 below;

1.56. "Territory" shall mean all the countries of the world;

1.57. "United States Dollar" and "US\$" shall mean the lawful currency for the time being of the United States of America;

B. *Interpretation.* In this Agreement the following shall apply:

(1) The singular includes the plural and vice versa, the masculine includes the feminine and vice versa.

(2) Any reference to a Clause or Schedule shall, unless otherwise specifically provided, be to a Clause or Schedule of this Agreement.

(3) The headings of this Agreement are for ease of reference only and shall not affect its construction or interpretation.

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## 2. GRANT OF RIGHTS.

2.1. Subject to the terms and conditions contained herein and, in consideration of the payments specified under Clause 6.1, Elan hereby grants to Orasense for the Term a non-exclusive license, including the limited right to grant sublicenses pursuant to Clause 3 hereof, in the Field in the Territory to the Elan Intellectual Property to research, develop, make and have made, offer for sale, sell, import and export the Products (including Royalty Products) and the Oral Platform in the Field, subject to any contractual obligations of Elan to Independent Third Parties as of the Effective Date and, unless prohibited by the paragraph below titled *Non Competition*, contractual obligations to Independent Third Parties that Elan may enter into after the Effective Date (the "Elan License").

2.2. If Isis or Orasense reasonably believes that a Patent Controlled by Elan is necessary to practice in the Field and should be included in the Elan License, then Isis or Orasense, as the case may be, shall send a written request to Elan (with a sufficiently detailed explanation) to amend Schedule 1 so as to include such Patent in the Elan License. Elan agrees to consider such request in good faith and to promptly respond to Isis or Orasense, as the case may be. If Elan determines that the Patent Controlled by Elan is necessary to practice in the Field, then Elan, Orasense and Isis, as the case may be, shall, subject to any contractual obligations of Elan or rights of third parties in existence as of the Effective Date or at any time hereafter, amend Schedule 1 to include such Patent.

2.3. In the event, the Elan License granted to Orasense hereunder is restricted or limited by any contractual obligations of Elan or rights of any Independent Third Parties (a) at any time after the Effective Date or (b) as a result of a breach of the noncompetition provision under Clause 11 of the Original License Agreement, Elan shall use reasonable commercial efforts to exclude or, where applicable, to minimize any such restriction or limitation. Except as expressly provided herein, all proprietary rights and rights of ownership with respect to the Elan Intellectual Property shall at all times remain solely with Elan. For the avoidance of doubt, Elan shall not have any obligations to exclude or minimize any restrictions or limitations under any agreement between an Independent Third Party and Elan entered into prior to the Effective Date, unless such restrictions or limitations arise in connection with a breach by Elan of the noncompetition provision under Clause 11 of the Original License Agreement.

To the extent royalty or other compensation obligations to Independent Third Parties that are payable with respect to Elan Intellectual Property would be triggered by the use or proposed use of Elan Intellectual Property by Orasense, its Affiliates and/or sublicensees, Elan will inform Orasense and Isis of such royalty or compensation obligation. If Orasense decides to utilize the Elan Intellectual Property, then Orasense will be responsible for the payment of such royalty or other compensation obligations relating thereto.

2.4. Notwithstanding anything contained in this Agreement to the contrary, Elan shall have the right, and subject to the paragraph below titled Non-Competition, to fully exploit and grant licenses and sublicenses with respect to the Elan Intellectual Property. Elan's rights to exploit and grant licenses referred to in the immediately preceding sentence shall include, without limitation, the right to research, develop, license and Commercialize products.

2.5. Orasense shall not be permitted to (a) encumber any of its rights under the Elan License, except pursuant to Clause 3 below; (b) assign any of its rights under the Elan License or this Agreement, except pursuant to Clause 15 below; and/or (c) subject to Clause 3 below, sublicense any of its rights under the Elan License.

2.6. Orasense will use its reasonable commercial endeavors to exploit the Elan Intellectual Property, the Isis Intellectual Property and Orasense Collaboration Intellectual Property in accordance with this Agreement. Orasense shall employ diligent efforts to research, develop, register, and Commercialize the Product in the Territory.

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2.7. Orasense and its sublicensees, if any, shall be solely responsible for ensuring that the research, development, manufacture and Commercialization of the Products within each country of the Territory is strictly in accordance with all legal, regulatory requirements and applicable laws for each country of the Territory.

2.8. When Packaged, and to the extent permitted by law, a Label shall include an acknowledgement that the Product is made under license from Elan. Such acknowledgement shall take into consideration all regulatory requirements and applicable laws in each country of the Territory and Orasense's reasonable commercial requirements. Orasense shall wherever possible give due acknowledgement and recognition to Elan in all printed promotional and other material regarding the Product such as stating that the Product is under license from Elan and that the applicable Elan Intellectual Property has been applied to the Products. Orasense shall consult with and obtain the written approval of Elan as to the format and content of any promotional and other material insofar as it relates to a description of, or other reference to, the application of the Elan Intellectual Property, such approval not to be unreasonably withheld or delayed. The further consent of Elan shall not be required where the format and content of such materials is substantively similar as the materials previously furnished to and approved in writing by Elan.

### 3. **SUBLICENSES**

3.1. Orasense shall not sublicense any of its rights in or to the Elan Intellectual Property without the prior written consent of Elan, which consent may be withheld by Elan in its sole discretion; provided, however, that if such a sublicense is in connection with a bona fide drug development or Commercialization agreement ("Sublicense Agreement"), Orasense may so sublicense all or any part of its rights in and to the Elan Intellectual Property without Elan's consent, subject to the following terms and conditions:

3.1.1. Orasense will inform Elan of the identity of any sublicensee under a Sublicense Agreement and the nature of such Sublicense Agreement within 60 days of the execution of such Sublicense Agreement;

3.1.2. any Sublicense Agreement shall require such sublicensee to maintain the confidentiality of all information concerning the Elan Intellectual Property, such confidentiality obligations to be no less onerous than as set forth in Clause 7 hereof

3.1.3. Orasense shall remain responsible for all acts and omissions of any sub-licensee, as if they were acts and omissions by Orasense; and

3.1.4. the rights of any sublicensee (other than Isis) under any permitted Sublicense Agreement in and to the Elan Intellectual Property shall survive the termination of this Agreement; provided, however, that (i) such sublicense was granted in accordance with this Agreement; and (ii) nothing contained in this Agreement shall prohibit or restrict Elan from assigning or transferring to a third party or otherwise disposing of any of the Elan Intellectual Property in accordance with Clause 15 below.

### 4. **DEVELOPMENT OF ROYALTY PRODUCT**

4.1. Orasense shall, and shall cause its sublicensees to, diligently pursue the research and development of the Elan Intellectual Property, Isis Intellectual Property and Orasense Collaboration Intellectual Property and shall use its, and shall cause its sublicensees to use their, commercially reasonable efforts to Commercialize a Royalty Product.

4.2. At the request of Elan, the Parties will meet, not to exceed two times per year, to exchange [\*\*\*]

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### 5. **REGULATORY APPROVALS**

5.1. Orasense shall, or shall cause its sublicensees, at its or its sublicensees' sole cost and expense, to file and shall use its reasonable best efforts to prosecute to approval or cause its sublicensees to prosecute to approval, the Marketing Authorizations for the Products in the Territory. During any Marketing Authorization registration procedure, Orasense shall keep Elan promptly and fully advised of Orasense's registration activities, progress and procedures with respect to the Elan Intellectual Property and/or Orasense Collaboration Intellectual Property. Orasense shall, and shall cause its sublicensees to, inform Elan of any writings, dealings and other communications that Orasense and its sublicensees have with the FDA and any other Regulatory Authority with respect to the information covered by Section 4.2 above. The Parties shall collaborate in relation to obtaining any required approvals, including Regulatory Approval of any Regulatory Authority in each country in which Commercialization of any Royalty Product is sought for final Labeling.

5.2. Subject to agreement to the contrary, any and all Marketing Authorizations filed hereunder for Products shall, to the extent owned by Orasense, remain the property of Orasense, provided that Orasense shall allow Elan access thereto to enable Elan to research, develop and Commercialize any product outside the Field. Orasense shall maintain or cause its sublicensees to maintain such Marketing Authorizations at its or their own cost and expense.

5.3. Orasense and Isis shall indemnify and hold harmless Elan, its agents and employees from and against all claims, damages, losses, liabilities and expenses to which Elan, its agents, and employees may become subject related to or arising out of Orasense's bad faith, negligence or intentional misconduct in connection with the filing or maintenance of the Marketing Authorizations.

## 6. FINANCIAL PROVISIONS

6.1 In consideration of the license to the Patents licensed to Orasense by Elan under the Elan License, Orasense shall pay to Elan, the following amounts:

6.1.1 *Product Fees and Royalties.* Payments to Elan with respect to services rendered in connection with the Development Product and/or the Oral Platform shall be paid as provided in Clause (a); and (ii) net proceeds derived by Orasense, its Affiliates or sublicensees from Products, shall be allocated as set forth under Clauses (b) and (c).

(a) *Development Work.* Research and development work performed during the Research Term pursuant to the Research Plan contracted by Orasense to Elan shall be payable by Orasense to Elan based on fully burdened actual costs at Elan's Full Time Equivalent Rate, with annual Cost of Living Increases;

(b) *Primary Product Royalties.* Orasense will pay Elan a royalty on (i) any [\*\*\*] in connection with a Primary Royalty Product, including [\*\*\*] thereof; and (ii) the [\*\*\*] of any Primary Royalty Product. Such royalty will equal [\*\*\*] No royalties will be due on [\*\*\*] and

(c) *Secondary Product Royalties.* Orasense will pay Elan a royalty on (i) any [\*\*\*] in connection with a Secondary Royalty Product, including [\*\*\*] thereof; and (ii) the [\*\*\*] of any Secondary Royalty Product. Such royalty will equal [\*\*\*] provided, however, that Elan will not be entitled to any royalties in the event a Secondary Royalty Product (x) utilizes Know-How Controlled by [\*\*\*]; (y) does not utilize any Know-How Controlled by [\*\*\*] and (z) is administered to humans [\*\*\*] No royalties will be due on [\*\*\*] with respect to a Secondary Royalty Product.

6.2 Payments pursuant to Clauses 6.1.1 above, if any, shall be made semi annually in arrears within [\*\*\*] days after the expiry of the applicable period. The method of payment shall be by wire transfer to an account specified by Elan and shall be nonrefundable to Orasense. Each payment made

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to Elan shall be accompanied by a true accounting of all Royalty Products sold by Orasense, its Affiliates and its permitted sublicensees, if any, during such quarter. Such accounting shall show, on a country-by-country and Royalty Product-by-Royalty Product basis, Net Sales, royalties and/or milestones received by Orasense (and the calculation thereof) and each calculation of royalties with respect thereto, including the calculation of all adjustments and currency conversions.

6.3 Orasense shall maintain and keep clear, detailed, complete, accurate and separate records for a period of [\*\*\*] years following the completion of such records so: (i) as to enable any royalties which shall have accrued hereunder to be determined; and (ii) that any deductions made in arriving at the Net Sales can be determined.

6.4 All payments due hereunder shall be made in United States Dollars. Payments due on Net Sales of any Royalty Product, royalties or milestones received by Orasense with respect to any Royalty Product for each calendar quarter made in a currency other than United States Dollars shall first be calculated in the foreign currency and then converted to United States Dollars on the basis of the average exchange rate in effect for such quarter for the purchase of United States Dollars with such foreign currency quoted in the Wall Street Journal (or comparable publication if not quoted in the Wall Street Journal) with respect to the currency of the country of origin of such payment, determined by averaging the rates so quoted on each business day of such quarter.

6.5 If Orasense claims in good faith that one or more of its devices, products, parts or components thereof, compounds and/or drug products is not a Royalty Product, then Orasense shall within sixty (60) days of the date of receipt of any milestone payment or first commercial launch of any such devices, products, parts, or components thereof, or compounds notify Elan in writing and establish same to Elan's reasonable satisfaction.

6.6 If, at any time, legal restrictions in the Territory prevent the prompt payment when due of royalties or any portion thereof, the Parties shall meet to discuss suitable and reasonable alternative methods of reimbursing Elan the amount of such royalties. In the event that Orasense is prevented from making any payment under this Agreement by virtue of the statutes, laws, codes or government regulations of the country from which the payment is to be made, then such payments may be paid by depositing them in the currency in which they accrue to Elan's account in a bank acceptable to Elan in the country the currency of which is involved or as otherwise agreed by the Parties.

6.7 Elan and Orasense agree to co-operate in all respects necessary to take advantage of any double taxation agreements or similar agreements as may, from time to time, be available.

6.8 Any taxes payable by Elan on any payment made to Elan pursuant to this Agreement shall be for the account of Elan. If so required by applicable law, any payment made pursuant to this Agreement shall be made by Orasense after deduction of the appropriate withholding tax, in which event the Parties shall co-operate to obtain the appropriate tax clearance as soon as is practicable. On receipt of such clearance, Orasense shall forthwith procure that the amount so withheld is paid to Elan.

6.9 Orasense shall, not more than [\*\*\*] in each calendar year, permit Elan or its duly authorized representatives upon reasonable notice and at any reasonable time during normal business hours to have access to inspect and audit the accounts and records of Orasense and any other book, record, voucher, receipt or invoice relating to the calculation of the Royalty Payments submitted to Elan. Any such inspection of Orasense's records shall be at the expense of Elan, except that if any such inspection reveals a deficiency in the amount of the royalty actually paid to Elan hereunder in any calendar quarter of [\*\*\*] or more of the amount of any royalty actually due to Elan hereunder, then the expense of such inspection shall be borne solely by Orasense. Any amount of deficiency shall be paid promptly to Elan by Orasense. If such inspection reveals a surplus in the amount of royalties actually paid to Elan by Orasense, Elan shall reimburse Orasense the surplus within fifteen (15) days after determination.

6.10 In the event of any unresolved dispute regarding any alleged deficiency or overpayment of royalty payments hereunder, the matter will be subject to resolution in accordance with Clause 24.9 of the Development Agreement, which is incorporated by reference and shall for such purposes survive termination of the Development Agreement.

## 7. CONFIDENTIAL INFORMATION

7.1. The Parties acknowledge that it may be necessary, from time to time, to disclose to each other confidential and proprietary information, including without limitation, Patents, inventions, works of authorship, trade secrets, specifications, designs, data, Know-How and other information relating to the Field, the Products, Elan Intellectual Property, Isis Intellectual Property and Orasense Intellectual Property, as the case may be, processes, services and business of the disclosing Party. The foregoing shall be referred to collectively as "Confidential Information". Any Confidential Information revealed by a Party to another Party shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's obligations under this Agreement and the Development Agreement and for no other purpose.

7.2. Each Party agrees to disclose Confidential Information of another Party only to those employees, representatives and agents requiring knowledge thereof in connection with their duties directly related to the fulfilling of the Party's obligations under this Agreement. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information. Each Party agrees that it will exercise the same degree of care, but in no event less than a reasonable degree, and protection to preserve the proprietary and confidential nature of the Confidential Information disclosed by a Party, as the receiving Party would exercise to preserve its own proprietary and confidential information. Each Party agrees that it will, upon request of a Party, return all documents and any copies thereof containing Confidential Information belonging to or disclosed by, such Party.

7.3. Notwithstanding the above, each Party may use or disclose Confidential Information disclosed to it by another Party to the extent such use or disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, complying with patent applications, complying with applicable governmental regulations or otherwise submitting information to tax or other governmental authorities, conducting clinical trials, or making a permitted sub-license or otherwise exercising its rights hereunder, provided that if a Party is required to make any such disclosure of the other Party's Confidential Information, other than pursuant to a confidentiality agreement, such Party shall inform the recipient of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information.

7.4. Any breach of this Clause 7 by any of the Persons informed by one of the Parties is considered a breach by the Party itself.

7.5. Confidential Information shall not be deemed to include:

7.5.1. information that is generally available to the public;

7.5.2. information which is made public by the disclosing Party;

7.5.3. information which is independently developed by a Party as evidenced by such Party's written records, without the aid, application or use of the disclosing Party's Confidential Information;

7.5.4. information that is published or otherwise becomes part of the public domain without any disclosure by a Party, or on the part of a Party's directors, officers, agents, representatives or employees;

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7.5.5. information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis;

7.5.6. information which the receiving Party is required to disclose pursuant to:

7.5.6.1. a valid order of a court or other governmental body or any political subdivision thereof or otherwise required by law; or

7.5.6.2. any other requirement of law;

provided that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or other appropriate remedy concerning any such disclosure. The receiving Party shall fully cooperate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required;

7.5.7. information which was already in the possession of the receiving Party at the time of receiving such information, as evidenced by its written records, provided such information was not previously provided to the receiving Party from a source which was under an obligation to keep such information confidential; or

7.5.8. information that is the subject of a written permission to disclose, without restriction or limitation, by the disclosing Party.

7.6. The provisions relating to confidentiality in this Clause 7 shall remain in effect during the term of this Agreement, and for a period of [\*\*\*] years following the expiration or earlier termination of this Agreement but shall not apply to any information which a Party is required to file or otherwise disclose in accordance with requirements which are legally binding on it.

7.7. The Parties agree that the obligations of this Clause 7 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party expressly agrees that monetary damages would be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein. Accordingly, the Parties agree and acknowledge that any such violation or threatened violation will cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, any Party shall be entitled to obtain injunctive relief against the threatened breach of

the provisions of this Clause 7, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

7.8. Each of the Parties shall be entitled to provide a copy of this Agreement (and any subsequent amendments hereto) and the Development Agreement to a potential third party purchaser in connection with the sale of such Party's business or assets, including without limitation, in the case of Elan, the sale of the Elan Intellectual Property; provided that the relevant third party purchaser or assignee has entered into a confidentiality agreement on terms no less protective than the terms of this Clause 7.

## 8. WARRANTIES AND INDEMNITIES

8.1 Elan represents and warrants to Orasense as of the Original Effective Date that:

8.1.1 Elan is a corporation duly organized under the laws of its jurisdiction of organization and has all the requisite corporate power and authority to own and lease its respective properties,

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to carry on its respective business as presently conducted and as proposed to be conducted and to carry out the transactions contemplated hereby;

8.1.2 Elan has full corporate power and authority to enter into this Agreement and to perform its obligations hereunder, which have been duly authorized by all requisite corporate action of Elan. This Agreement is the valid and binding obligation of Elan, enforceable against it in accordance with its terms, except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and by general equity principles and limitations on the availability of equitable relief, including specific performance;

8.1.3 the execution, delivery and performance by Elan of this Agreement will not: (i) violate any provision of applicable law, statute, rule or regulation known by and applicable to Elan or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to Elan or any of its properties or assets; or (ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under the charter or organizational documents of Elan to which Elan is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have an adverse material effect on the business, assets, liabilities (contingent or otherwise), operations, condition (financial or otherwise), or prospects of Elan;

8.1.4 to Elan's best knowledge, except as set forth on Schedule 3 hereto, (i) Elan has the right to grant the Elan License, (ii) there are no agreements between Elan and any third parties that conflict with the Elan License which would have a material adverse effect on the ability of Orasense to conduct its business as presently proposed to be conducted, (iii) Elan is the owner or licensee of all rights, title and interest in the Elan Intellectual Property; and (v) [\*\*\*]

8.2 Orasense represents and warrants to Elan as of the Original Effective Date that:

8.2.1 Orasense is duly and validly existing in good standing in the jurisdiction of its incorporation and each other jurisdiction in which the conduct of its business requires such qualification (except where such failure to so qualify shall not have a material adverse effect on the business and assets of Orasense), and Orasense is in compliance with all applicable laws, rules, regulations or orders relating to its business and assets;

8.2.2 Orasense has full corporate authority to execute and deliver this Agreement and to consummate the transactions contemplated hereby; this Agreement has been duly executed and delivered and constitutes the legal and valid obligations of Orasense and is enforceable against Orasense in accordance with its terms; and the execution, delivery and performance of this Agreement and the transactions contemplated hereby will not violate or result in a default under or creation of lien or encumbrance under Orasense's certificate of incorporation, by-laws or other organizational documents, any material agreement or instrument binding upon or affecting Orasense, or its properties or assets or any applicable laws, rules, regulations or orders affecting Orasense or its properties or assets;

8.2.3 Orasense is not in default of its charter or by-laws, any applicable laws or regulations or any material contract or agreement binding upon or affecting it or its properties or assets and the execution, delivery and performance of this Agreement and the transactions contemplated hereby will not result in any such violation;

8.2.4 Orasense represents and warrants to Elan that the execution of this Agreement by Orasense and the full performance and enjoyment of the rights of Orasense under this Agreement will not breach the terms and conditions of any license, contract, understanding or agreement, whether express, implied, written or oral between Orasense and any third party;

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8.2.5 Orasense represents and warrants to and covenants with Elan that it has the sole, exclusive and unencumbered right to grant the licenses and rights herein granted to Elan and that it has not granted and will not grant any option, license, right or interest in or to the Elan Intellectual Property, the Orasense Collaboration Intellectual Property, or other property to any third party which would conflict with the rights granted by this Agreement;

8.2.6 the Products shall be developed, manufactured, transported, stored, handled, Packaged, marketed, promoted, distributed, offered for sale, sold and otherwise Commercialized in accordance with all regulations and requirements of the FDA and foreign governmental authorities having jurisdiction in such country or countries in the Territory including, without limitation, cGCP, cGLP, cGMP regulations.

8.2.7 the Products shall not be adulterated or misbranded as defined by the Federal Food, Drug and Cosmetic Act (or applicable foreign law) and shall not be a product which would violate any section of such Act if introduced in interstate commerce;



8.2.8 it is fully cognizant of all applicable statutes, ordinances and regulations of the United States of America and countries in the Territory with respect to the manufacture of the Products including, but not limited to, the U.S. Federal Food, Drug and Cosmetic Act and regulations thereunder and similar statutes in countries outside of the United States. Orasense shall manufacture or procure the manufacture of the Products in conformity with the Marketing Authorizations and in a manner which fully complies with all United States of America and foreign statutes, ordinances, regulations and practices.

8.3 In addition to any other indemnifications provided for herein, Elan shall indemnify and hold harmless Orasense and its Affiliates and their respective employees, agents, partners, officers and directors from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by Orasense arising out of or in connection with any (a) breach of any representation, covenant, warranty or obligation by Elan hereunder, or (b) any act or omission on the part of Elan or any of its agents or employees in the performance of this Agreement.

8.4 In addition to any other indemnifications provided for herein, Orasense and Isis and any of their respective sublicensees shall indemnify and hold harmless Elan and its Affiliates, and each of Elan's and its Affiliates' respective employees, agents, partners, officers and directors (each an "Indemnified Party") from and against any claims, losses, liabilities or damages (including reasonable attorney's fees and expenses) incurred or sustained by an Indemnified Party arising out of or in connection with any (a) breach of any representation, covenant, warranty or obligation by Orasense or its sublicensees hereunder, or (b) any act or omission on the part of Orasense, Isis or any of their respective sublicensees in connection with the research, development, manufacture and/or Commercialization of any Product hereunder, including without limitation, with respect to the conduct of any clinical trials and death or injury to any person.

8.5 Orasense and Isis shall each obtain prior to conducting any clinical trial in respect of the Product appropriate comprehensive general liability insurance and/or other insurance coverage (the "Policies"), and shall each maintain such Policies during such clinical trials and for a period of five years thereafter. Orasense and Isis shall furnish Elan with copies of all Policies that it holds in respect of such clinical trials.

8.6 Any Party seeking an indemnity hereunder shall:

8.6.1 fully and promptly notify the other Party of any claim or proceeding, or threatened claim or proceeding;

8.6.2 permit the indemnifying Party to take full care and control of such claim or proceeding;

8.6.3 cooperate in the investigation and defense of such claim or proceeding;

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8.6.4 not compromise or otherwise settle any such claim or proceeding without the prior written consent of the other Party, which consent shall not be unreasonably withheld, conditioned or delayed; and

8.6.5 take all reasonable steps to mitigate any loss or liability in respect of any such claim or proceeding.

**8.7 NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, NEITHER ELAN NOR ORASENSE SHALL BE LIABLE TO THE OTHER PARTY, BY REASON OF ANY REPRESENTATION OR WARRANTY, CONDITION OR OTHER TERM OR ANY DUTY OF COMMON LAW, OR UNDER THE EXPRESS TERMS OF THIS AGREEMENT, FOR ANY CONSEQUENTIAL, SPECIAL OR INCIDENTAL LOSS OR DAMAGE (WHETHER FOR LOSS OF PROFIT OR OTHERWISE) AND WHETHER OCCASIONED BY THE APPLICABLE PARTY'S NEGLIGENCE OR OF ITS EMPLOYEES OR AGENTS OR OTHERWISE.**

**8.8 EXCEPT AS SET FORTH IN THIS CLAUSE 8, ELAN IS GRANTING THE ELAN LICENSE HEREUNDER ON AN "AS IS" BASIS WITHOUT RECOURSE, REPRESENTATION OR WARRANTY WHETHER EXPRESS OR IMPLIED, INCLUDING WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR INFRINGEMENT OF THIRD PARTY RIGHTS, AND ALL SUCH WARRANTIES ARE EXPRESSLY DISCLAIMED.**

## **9 INTELLECTUAL PROPERTY OWNERSHIP RIGHTS**

9.1 Title and all other ownership rights, including patent rights, relating to the Elan Intellectual Property shall belong to Elan.

9.2 Each Party shall own the legal and equitable title to any invention invented by such Party that is not Orasense Intellectual Property.

9.3 Orasense shall permanently mark or otherwise use reasonable efforts to cause any third party to permanently mark all Products and/or the Packaging therefor with such license or patent notices to comply with the applicable laws of each country of sale of the Territory or otherwise to generally communicate the existence of any of Patents under the Elan Intellectual Property for the countries of the Territory and in such manner as Elan may reasonably request in writing following receipt of written notice by Orasense of its intent to Commercialize a Product.

9.4 Elan shall have the sole and exclusive right to (i) secure any Patents under the Elan Intellectual Property; (ii) defend all Patents under the Elan Intellectual Property against third party oppositions; and (iii) maintain in force any material issued letters patent within the Patents under the Elan Intellectual Property. Elan shall have the sole right, in its discretion, to control such filing, prosecution, defense and maintenance of any Patents under the Elan Intellectual Property.

9.5 In the event that Elan informs Orasense and Isis that it does not intend to file patent applications on patentable inventions and discoveries within the Elan Intellectual Property that relate to the Field in one or more countries in the Territory or fails to file such an application within a reasonable period of time, Orasense shall have the option at its expense to file and prosecute such patent application(s) in the joint names of Orasense and Elan unless Elan believes that the prosecution and maintenance of any such Patent may be harmful to Elan's or its Affiliates' general patent strategy, business objectives, or is illegal or without adequate foundation. Subject to the preceding sentence, Elan shall reasonably cooperate with Orasense at Orasense's sole cost and expense and shall execute such documents as are reasonably necessary to continue the prosecution and maintenance of such patent application.

9.6 Orasense, Isis and Elan shall promptly inform each other in writing of any alleged infringement of any patents within the Patents within the Elan Intellectual Property and the Orasense Intellectual Property or any alleged misappropriation of trade secrets within the Elan Intellectual

Property or the Orasense Intellectual Property by a third party of which it becomes aware and provide the others with any available evidence of such infringement or misappropriation insofar as such infringements or misappropriation relate solely to the Field.

9.7 Orasense shall have the right to prosecute at its own expense and for its own benefit any infringements of the Patents within the Elan Intellectual Property or misappropriation of the Elan Intellectual Property, insofar as such infringements or misappropriation relate solely to the Field. In the event that Orasense takes such action, Orasense shall do so at its own cost and expense. At Orasense's request, Elan shall cooperate with such action. Any recovery in relation to such infringement proceeding shall belong to Orasense. Should Orasense decide not to pursue such infringers, within a reasonable period but in any event within [\*\*\*] days after receiving written notice of such alleged infringement or misappropriation Elan may in its discretion initiate such proceedings in its own name, at its expense and for its own benefit, and at Elan's request, Orasense shall cooperate with such action. Alternatively, Orasense and Elan may agree to institute such proceedings in their joint names and shall reach agreement as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party. If the infringement of the Patents within the Elan Intellectual Property affects both the Field as well as other products being developed or commercialized by Elan or its commercial partners outside the Field, Orasense and Elan shall endeavor to agree as to the manner in which the proceedings should be instituted and as to the proportion in which they shall share the proceeds of any such proceedings, and the expense of any costs not recovered, or the costs or damages payable to the third party.

## 10 RIGHTS EXPLOITATION OUTSIDE THE FIELD

10.1 *Licenses to Orasense Collaboration Intellectual Property.* Subject to the Non-Competition provisions in Clause 11 hereof, Orasense hereby grants to Elan a royalty free and fully sublicensable [\*\*\*] license with Isis [\*\*\*] in the Territory, to practice Orasense Collaboration Intellectual Property, such license to expire, on a country-by-country and Product-by-Product basis, upon the date of (i) the last to expire Patent under the Orasense Collaboration Intellectual Property; or (ii) [\*\*\*] years from the first commercial sale of a product incorporating the Orasense Collaboration Intellectual Property, whichever is later.

10.2 [\*\*\*].

## 11 NON-COMPETITION

During [\*\*\*], Elan shall not develop or Commercialize, or assist in the development or Commercialization of an [\*\*\*], except (a) for or on behalf of Orasense, or (b) with the prior written, unanimous consent of the Management Committee. During the Research Term and provided that Orasense is maintaining an active program for the development and Commercialization of the Development Candidate in the Field, Elan shall not develop or Commercialize or assist in the development for Commercialization of [\*\*\*] Nothing contained herein shall be construed as (i) limiting the activities of an existing third party licensee of Elan from developing Oligonucleotide Drugs utilizing Elan Intellectual Property to the extent such rights have been previously granted by Elan, provided Elan does not provide any active support to any such activities in excess of its existing contractual obligations or (ii) prohibiting Elan from licensing Elan Intellectual Property to an Independent Third Party or limiting the activities of any such future Independent Third Party licensee of Elan from developing [\*\*\*] utilizing Elan Intellectual Property [\*\*\*].

## 12 TERM AND TERMINATION OF AGREEMENT

12.1 The term of this Agreement and the term of the Licenses granted hereunder with respect to a Product utilizing or based on the Licensed Technologies shall commence as of the Effective Date and continue, on a Product-by-Product basis and country by country basis, for the life of the Patent rights upon which such Product is based on or utilizes in such country (the "Term"); provided, however, that

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all royalty and fee obligations contained herein shall survive for the greater of (i) the Term or (ii) [\*\*\*] years from the first commercial sale of such Product.

12.2 Nothing contained herein shall obligate or restrict any party from utilizing public, non-proprietary information which is not subject to the protection of applicable patent laws.

12.3 If any Party breaches any material provision of this Agreement and if such breach is (i) not capable of being cured or (ii) is capable of being cured but is not [\*\*\*] after the non-breaching Party gives written notice of the breach to the breaching Party, the non-breaching Party may terminate this Agreement immediately by giving notice of the termination to the breaching Party, effective on the date of the notice, **provided, however**, that (x) so long as the breaching Party takes substantial steps to cure the breach promptly after receiving notice of the breach from the non-breaching party and thereafter diligently prosecutes the cure to completion as soon as is practicable, the non-breaching Party may not terminate this Agreement so long as the breaching party is acting in good faith to rectify such breach, or (y) the default involves a good faith dispute regarding the amount of any required payment, provided any undisputed amount is timely paid, such default shall be stayed and the remainder may be withheld so long as the withholding Party is proceeding in good faith to resolve the dispute.

12.4 In the event that the Isis License Agreement shall be terminated, at the sole option of Elan and upon written notice to Isis and Orasense, the Elan License shall be immediately terminated.

12.5 Upon the occurrence of an Event of Bankruptcy with respect to Orasense, Isis or Elan, the other Party may, upon written notice to Isis and the Party with respect to which such Event of Bankruptcy has occurred, immediately terminate the Elan License. As used in this Clause 12.5, the term "Event of Bankruptcy" relating to either Orasense or Elan shall mean:

12.5.1 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of either Party of it or over all or a substantial part of its assets under the law of any applicable jurisdiction, including without limit, Bermuda, the United States of America or Ireland; or

12.5.2 an application or petition for bankruptcy, corporate re-organization, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limit, Bermuda, the United States of America or

Ireland (other than as part of a bona fide restructuring or reorganization), is filed, and is not discharged within [\*\*\*] days, or if either Party applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of either Party are for any reason seized, confiscated or condemned.

12.6 Upon exercise of those rights of termination as specified in Clause 12.1 to Clause 12.5 inclusive or elsewhere within this Agreement, this Agreement shall, subject to the other provisions of this Agreement, automatically terminate forthwith and be of no further legal force or effect.

12.7 Upon expiration or termination of the Agreement:

12.7.1 any sums that were due from Orasense to Elan under Clause 6, including without limitation on Net Sales, in the Territory or in such particular country or countries in the Territory (as the case may be) prior to the expiration or termination of this Agreement as set forth herein shall be paid in full within [\*\*\*] days after the expiration or termination of this Agreement for the Territory or for such particular country or countries in the Territory (as the case may be);

12.7.2 any provisions clearly meant to survive termination or expiration of this Agreement, including without limitation Clause 7, shall remain in full force and effect;

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12.7.3 all representations, warranties and indemnities shall insofar as are appropriate remain in full force and effect;

12.7.4 the rights of inspection and audit set out in Clause 12.6 shall continue in force for a period of [\*\*\*]

12.7.5 termination of this Agreement for any reason shall not release any Party hereto from any liability which, at the time of such termination, has already accrued to the other Party or which is attributable to a period prior to such termination nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement;

12.7.6 the Elan Intellectual Property and all rights, licenses and sublicenses granted by Elan in and pursuant to this Agreement shall cease for the Territory or for such particular country or countries in the Territory (as the case may be) and shall immediately revert to Elan. Following such expiration or termination, Orasense may not thereafter use in the Territory or in such particular country or countries in the Territory (as the case may be) (a) any valid and unexpired Patents in the Elan Intellectual Property and/or (b) any Elan Intellectual Property that remains confidential or otherwise proprietary to Elan. All rights to Orasense Intellectual Property will be transferred to and owned by Orasense. Rights of permitted Independent Third Party sublicensees in and to the Elan Intellectual Property shall survive the termination of the license and sublicense agreements granting said intellectual property rights to Orasense; and Orasense, Elan and Isis shall in good faith agree upon the form most advantageous to Isis and Elan in which the rights of the sublicensor under any such sublicenses are to be held (which form may include continuation of Orasense solely as the holder of such licenses or assignment of such rights to a third party or parties, including an assignment to both Elan and Isis). Any sublicense agreement between Orasense and such permitted sublicensee shall permit an assignment of rights by Orasense to Elan and shall contain additional reasonable confidentiality protections which an assignee shall reasonably require. Upon any such assignment, Isis and Elan shall enter into good faith negotiations with respect to additional reasonable confidentiality protections which either party shall reasonably require.

## 13 **FORCE MAJEURE**

13.1 Neither Party to this Agreement shall be liable for delay in the performance of any of its obligations hereunder if such delay results from causes beyond its reasonable control, including, without limitation, acts of God, fires, strikes, acts of war, or intervention of a government authority, non availability of raw materials, but any such delay or failure shall be remedied by such Party as soon as practicable; provided, however, that neither party hereunder shall be excused for delay in the performance of any of its payment obligations hereunder.

## 14 **SETTLEMENT OF DISPUTES; GOVERNING LAW**

14.1 Any dispute between the Parties arising out of or relating to this Agreement will be subject to resolution in accordance with Clause 24.9 of the Development Agreement, which is incorporated by reference and shall for such purposes survive termination of the Development Agreement.

14.2 This Agreement is construed under and ruled by the laws of the State of New York, without regard to the conflict of law principles.

## 15 **ASSIGNMENT**

This Agreement may not be assigned by either Party without the prior written consent of the other, which consent shall not be unreasonably withheld, conditioned or delayed, save that (i) either Party may assign this Agreement to its Affiliate without such consent, provided that such assignment does not have any adverse tax consequences on the other Party, and (ii) Elan may assign its rights and

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obligations hereunder in connection with a sale of its business or sale of any of the Elan Intellectual Property licensed hereunder, whether by merger, sale of stock, sale of assets or otherwise. Elan and Orasense will discuss any assignment by either Party to an Affiliate prior to its implementation in order to avoid or reduce any additional tax liability to the other Party resulting solely from different tax law provisions applying after such assignment to an Affiliate. For the purpose hereof, an additional tax liability shall be deemed to have occurred if either Party would be subject to a higher net tax on payments made hereunder after taking into account any applicable tax treaty and available tax credits than such Party was subject to before the proposed assignment. Notwithstanding any assignment hereof to an Affiliate, each Party will remain fully liable hereunder.

## 16 **NOTICES**

16.1 Any notice to be given under this Agreement shall be sent in writing in English by registered airmail or telefaxed to the following addresses:

If to Orasense at: Orasense Ltd.  
c/o Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: Ms. Lynne Parshall  
Telephone: (760) 603-2460  
Telefax: (760) 931-9639

If to Isis to: Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: Ms Lynne Parshall  
Telephone: (760) 603-2460  
Telefax: (760) 931-9639

with a copy to: Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: Grantland E. Bryce  
Telephone: 760-603-2707  
Fax: 760-268-4922

If to Elan at: Elan Corporation, plc  
C/o Elan International Services, Ltd.  
102 St. James Court  
Flatts,  
Smiths FL04  
Bermuda  
Attention: Secretary  
Telephone: 441 292 9169  
Fax: 441 292 2224

or to such other address(es) and telefax numbers as may from time to time be notified by either Party to the other hereunder.

16.2 All notices and other communications given to any Party hereto in accordance with the provisions of this Agreement will be deemed to have been given on the date of receipt if delivered by hand or overnight courier service or sent by confirmed teletype to such Party as provided in this Clause

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or in accordance with the latest unrevoked direction from such Party given in accordance with this Clause 16.

## 17 MISCELLANEOUS CLAUSES

17.1 No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any other breach or failure to perform or of any other right arising under this Agreement.

17.2 If any provision in this Agreement is agreed by the Parties to be, or is deemed to be, or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto,

17.2.1 such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable or, if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of such agreement or such earlier date as the Parties may agree; and

17.2.2 the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

17.3 The Parties shall use their respective reasonable endeavors to ensure that the Parties and any necessary third party shall execute and perform all such further deeds, documents, assurances, acts and things as any of the Parties hereto may reasonably require by notice in writing to the other Party or such third party to carry the provisions of this Agreement.

17.4 This Agreement shall be binding upon and inure to the benefit of the Parties hereto, their successors and permitted assigns and sublicensees.

17.5 No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between the Parties unless specifically referred to, and solely to the extent provided, in any such other agreement. In the event of a conflict between the provisions of this Agreement and the provisions of the Development Agreement, the terms of this Agreement shall prevail.

17.6 No amendment, modification or addition hereto shall be effective or binding on either Party unless set forth in writing and executed by a duly authorized representative of each Party. Amendments hereto shall be subject to the prior approval of Elan, which approval shall not be unreasonably withheld or delayed.

17.7 This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

17.8 Each of the Parties undertakes to do all things reasonably within its power which are necessary or desirable to give effect to the spirit and intent of this Agreement.

17.9 Each of the Parties hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty save as expressly set out herein or in any document referred to herein.

17.10 Nothing contained in this Agreement is intended or is to be construed to constitute Elan, Isis and Orasense as partners, or Isis as an employee of Orasense and Elan, or Orasense and Elan as an employee of Isis. Neither Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of the other Party or to bind the other Party to any contract, agreement or undertaking with any third party.

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**IN WITNESS WHEREOF**, the Parties hereto have executed this Agreement as of the date first set forth above.

**ELAN CORPORATION, PLC**

**ISIS PHARMACEUTICAL, INC.**

By: /s/ KEVIN INSLEY

By: /s/ B. LYNNE PARSHALL

Kevin Insley

B. Lynne Parshall

Name

Name

Title Authorized Signatory

Title Executive VP, CFO, Director

Date

Date

**ORASENSE, LTD.**

By: /s/ E.C. (NED) JACKSON

E.C. (Ned) Jackson

Name

Title

Date

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**SCHEDULE 1**

**ELAN PATENTS**

[\*\*\*]

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**SCHEDULE 2**

**ORASENSE COLLABORATION INTELLECTUAL PROPERTY**

[\*\*\*]

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QuickLinks

[AMENDED AND RESTATED LICENSE AGREEMENT BY AND BETWEEN ORASENSE LTD A Bermuda Limited Company ISIS PHARMACEUTICALS, INC A Delaware Corporation AND ELAN CORPORATION, PLC A Public Irish Company October 24, 2002](#)

JDOA  
Execution Copy (V8)  
24 October 2002

AMENDED AND RESTATED  
SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT

ELAN CORPORATION, PLC  
ELAN INTERNATIONAL SERVICES, LTD.

ISIS PHARMACEUTICALS, INC.

AND

ORASENSE LTD.

October 24, 2002

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THIS AMENDED AND RESTATED SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT is made this 24<sup>th</sup> day of October 2002,

among:

(1) **ELAN CORPORATION, PLC**, a public limited company incorporated under the laws of Ireland, and having its registered office at Lincoln House, Lincoln Place, Dublin 2, Ireland ("**Elan**");

(2) **ELAN INTERNATIONAL SERVICES, LTD.**, a private limited company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("**EIS**");

(3) **ISIS PHARMACEUTICALS, INC.**, a corporation incorporated under the laws of Delaware and having its principal place of business at 2292 Faraday Avenue, Carlsbad, CA 92008, United States of America ("**Isis**"); and

(4) **ORASENSE LTD.**, a private limited company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("**Orasense**").

**RECITALS:**

Capitalized terms shall have the meanings set forth below unless otherwise defined.

D. As of the date hereof, Elan (as defined below) has entered into the Elan License Agreement with Orasense and Isis, and Isis has entered into the Isis License Agreement with Orasense and Elan, in connection with the license to Orasense of the Elan Intellectual Property and the Isis Intellectual Property, respectively.

E. Elan and Isis have agreed to co-operate in the management of Orasense for the research, development and Commercialization of the Product based on their respective technologies.

F. Elan, EIS, Isis and Orasense are parties to that certain Subscription, Joint Development and Operating Agreement (the "Original Agreement") dated April 20, 1999 (the "Original Effective Date"). The parties have agreed to enter into this Agreement for the purpose of amending and restating the Original Agreement and recording the terms and conditions of the joint venture and of regulating their relationship with each other and certain aspects of the affairs of and their dealings with Orasense.

**NOW IT IS HEREBY AGREED AS FOLLOWS:**

**CLAUSE 1**

**DEFINITIONS**

1.1 In this Agreement, the following terms shall, where not inconsistent with the context, have the following meanings respectively.

"**Affiliate**" shall mean, with respect to Isis or Elan, any corporation or entity other than Orasense (and entities controlled by it) controlling, controlled or under the common control of Isis or Elan, as the case may be, and, with respect to Orasense, any corporation or entity under control of Orasense, but excluding, in the case of Elan, an Elan JV. A corporation or non-corporate entity shall be regarded as in control of another corporation if it owns or directly or indirectly

controls at least fifty percent (50%) of the voting stock of the other corporation or (a) in the absence of the ownership of at least fifty percent (50%) of the voting stock of a corporation or (b) in the case of a non-corporate entity, the power to direct or cause the direction of the management and policies of such corporation or non-corporate entity, as applicable.

"**Agreement**" shall mean this amended and restated agreement (which expression shall be deemed to include the Recitals and the Schedules hereto).

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"**Business**" shall mean the business of Orasense as described in Clause 2 and as more particularly specified in the Research Plan and such other business as the Directors may agree from time to time in writing should be carried on by Orasense.

"**Commercialization**" shall mean the manufacture, promotion, distribution, marketing and sale of the Products.

"**Common Stock**" shall mean the common stock, par value \$1.00 per share of Orasense.

"**Common Stock Equivalents**" shall mean any options, warrants, rights or any other securities convertible, exercisable or exchangeable, in whole or in part, for or into Common Stock.

"**Control**" shall mean the ability of Elan, Isis or Orasense, as the case may be, to grant a license or sublicense as contemplated herein without having to obtain the prior consent of any third party or having to amend any agreement between Elan, Isis or Orasense, as the case may be, and a third party.

"**Development Candidate**" shall mean, ISIS 104838, [\*\*\*] TNF-a, as more specifically detailed in the License Agreements.

"**Development Product**" shall mean any product containing as an active ingredient the Development Candidate formulated using the Oral Platform for humans.

"**Directors**" shall mean, at any time, the directors of Orasense.

"**EIS Director**" shall have the meaning set forth in Clause 7.

"**Elan Intellectual Property**" shall have the meaning set forth in the Elan License Agreement.

"**Elan License**" shall have the meaning set forth in the Elan License Agreement.

"**Elan License Agreement**" shall mean the amended and restated license agreement between Elan, Orasense and Isis, of even date herewith.

"**Elan Minority Interest**" will be deemed to have occurred if at any time after [\*\*\*], Elan's ownership interest in Orasense falls below [\*\*\*]

"**Encumbrance**" shall mean any liens, charges, encumbrances, equities, claims, options, proxies, pledges, security interests, or other similar rights of any nature.

"**Exchange Act**" shall mean the Securities Exchange Act of 1934, as amended.

"**Failure to Fund**" shall have the meaning set forth in Section 9.5.

"**Field**" shall mean the research, development and Commercialization of the Oral Platform for use with Oligonucleotide Drugs.

"**Financial Year**" means each year commencing on January 1 (or in the case of the first Financial Year, the date hereof) and expiring on December 31 of each year.

"**Fully Diluted Common Stock**" shall mean all of the issued and outstanding Common Stock, assuming the conversion, exercise or exchange of all outstanding Common Stock Equivalents.

"**Independent Third Party**" shall mean any person other than Orasense, Isis, Elan or any of their respective Affiliates.

"**Isis Blocking Invention**" shall mean [\*\*\*]

"**Isis Delivery Technology**" shall have the meaning given to such term in the Isis License Agreement.

"**Isis Directors**" has the meaning set forth in Clause 7.

"**Isis Intellectual Property**" shall have the meaning set forth in the Isis License Agreement.

"**Isis License**" shall have the meaning set forth in the Isis License Agreement.

"**Isis License Agreement**" shall mean the amended and restated license agreement between Isis, Orasense and Elan, of even date herewith.

"**Isis Oligonucleotide Drug**" shall mean any Oligonucleotide Drug Controlled by Isis other than the Development Candidate.

"**Know-How**" shall mean any and all rights to any discovery, invention (whether or not patentable), know-how, substances, data, techniques, processes, systems, formulations and designs which is not generally known to the public.

"**License Agreements**" shall mean the Elan License Agreement and the Isis License Agreement.

"**Licensed Technologies**" shall mean together, the Elan Intellectual Property and the Isis Intellectual Property.

"**Oligonucleotide Drug**" shall mean any single stranded [\*\*\*] at physiological pH oligonucleotide including those with [\*\*\*] used as a human therapeutic and/or prophylactic compound containing between [\*\*\*] nucleotides and/or nucleosides including oligonucleotide analogs which may include [\*\*\*]. For purposes of this agreement, Oligonucleotide Drug shall specifically exclude oligonucleotides used in [\*\*\*], oligonucleotides used [\*\*\*] an oligonucleotide, oligonucleotides used as [\*\*\*] or oligonucleotides used as [\*\*\*].

"**Oral**" shall mean administration by way of the mouth for the purpose of topical or systemic delivery by way of the alimentary canal.

"**Oral Platform**" shall mean formulation and excipient systems and technologies [\*\*\*] which use [\*\*\*] to develop dosage forms of drugs and deliver said dosage forms to the [\*\*\*] to achieve a local or systemic therapeutic effect.

"**Orasense Memorandum of Association and Bye-Laws**" shall mean the Memorandum of Association and Bye-Laws of Orasense.

"**Orasense Blocking Invention**" shall mean [\*\*\*]

"**Orasense Collaboration Intellectual Property**" shall mean (a) Know-How Controlled by Orasense through the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made on or before the end of the Research Term, and/or (c) inventions and Patents issued thereon developed by Orasense, Isis and/or Elan on behalf of Orasense (or any third party under contract with Orasense, Isis and/or Elan) or otherwise under the Original Research Plan or the Research Plan. Schedule 1 to this Agreement shall contain, by way of illustration but not limitation, examples of Orasense Collaboration Intellectual Property. At the end of the Research Term, the Parties shall amend Schedule 1 as may be necessary. For the avoidance of doubt, Orasense Collaboration Intellectual Property does not include any Patents and/or Know-How Controlled by Elan or Isis, as the case may be.

"**Orasense Intellectual Property**" shall mean Orasense Collaboration Intellectual Property and Orasense Post Collaboration Intellectual Property.

"**Orasense Post-Collaboration Intellectual Property**" shall mean (a) Know-How Controlled by Orasense after the end of the Research Term, (b) Patents Controlled by Orasense claiming inventions made after the end of the Research Term, and/or (c) inventions and Patents issued thereon made by Isis on Orasense's behalf after a Failure to Fund. For the avoidance of doubt, Orasense Post-Collaboration Intellectual Property does not include any Patents and/or Know-How Controlled by Elan or Isis, as the case may be.

"**Original Research Plan**" means the Research and Development Program under the Original Agreement.

"**Participant**" means Isis or Elan, as the case may be, and "Participants" means both of the Participants together.

"**Party**" means Elan, Isis, or Orasense, as the case may be, and "Parties" means all three together.

"**Patents**" shall mean any and all patents and patent applications. Patents shall also include all extensions, continuations, divisionals, patents-of-additions, re-examinations, re-issues, supplementary protection certificates and foreign counterparts of such patents and patent applications and any patents issuing thereon and extensions of any patents licensed hereunder.

"**Person**" means an individual, partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture, governmental entity or authority or other entity of whatever nature.

"**Permitted Transferee**" means any Affiliate or subsidiary of Elan, EIS or Isis, to whom this Agreement may be assigned, in whole or in part, pursuant to the terms hereof or in the case of Elan/EIS, an off-balance sheet special purpose entity created by Elan or EIS.

"**Product**" shall mean any drug under development or developed by or on behalf of Orasense made or formulated using the Isis Delivery Technology, the Elan Intellectual Property and/or the Orasense Intellectual Property for administration to humans.

"**Registration Rights Agreements**" means the Registration Rights Agreements dated April 20, 1999 relating to securities of Isis and Orasense, respectively.

"**Regulatory Application**" shall mean a regulatory application or other application (including any supplements or amendments thereto) required to be filed or filed with a Regulatory Authority in a country in connection with the Commercialization of a pharmaceutical product in such country.

"**Regulatory Approval**" means the final approval required to Commercialize a Product in each country of the Territory, and any other approval which is required to launch a product in the normal course of business.

"**Research Plan**" shall mean the program of development, including a budget, attached hereto as Schedule 2 which is hereby agreed to by Elan and Isis as of the Effective Date, with respect to the research, development, and commercialization of the Oral Platform and the Development Candidate.

"**Research Term**" shall mean the period commencing on [\*\*\*] and continuing through [\*\*\*], and any extension thereto by the mutual agreement of Isis and Elan.

"**Regulatory Authority**" shall mean any regulatory authority outside the United States of America, the approval of which is necessary to market a Product.

"**Securities Act**" means the Securities Act of 1933, as amended.

"**Shares**" means the shares of Common Stock of Orasense.



"**Stockholder**" means any of EIS, Isis, any Permitted Transferee or any other Person who subsequently becomes bound by this Agreement as a holder of the Shares, and "**Stockholders**" means all of the Stockholders together.

"**Term**" shall mean the term of this Agreement.

"**Territory**" shall mean all of the countries of the world.

"**Third Party Oligonucleotide Drug**" shall mean any Oligonucleotide Drugs Controlled solely by an Independent Third Party, other than an Isis Oligonucleotide Drug.

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"**Third Party Product**" shall mean Products based upon Third Party Oligonucleotide Drugs that are made, designed, or otherwise created by or on behalf of an Independent Third Party after the Effective Date using the Orasense Collaboration Intellectual Property and/or the Licensed Technologies. For avoidance of doubt, any Product based upon an Oligonucleotide Drug jointly developed by an Independent Third Party and Isis other than pursuant to the Research Plan shall be deemed to be an Isis Product; provided, however, that such Third Party Product does not incorporate or otherwise utilize Orasense Collaboration Intellectual Property or Elan Intellectual Property.

"**Transaction Documents**" means this Agreement, the Elan License Agreement, the Isis License Agreement, the Registration Rights Agreements and associated documentation of even date herewith, by and between Isis, Elan, EIS and Orasense, as applicable.

"**United States Dollar**" and "**US\$**" and "**\$**" means the lawful currency of the United States of America.

1.2 In addition, the following definitions have the meanings in the Clauses corresponding thereto, as set forth below.

Definitions	Clause
" <b>Buyout Option</b> "	20.1
" <b>Closing</b> "	4.2
" <b>Confidential Information</b> "	22.1
" <b>EIS Director</b> "	7.2
" <b>Elan Valuation</b> "	20.2
" <b>Indemnified Party</b> "	10.6
" <b>Isis Directors</b> "	7.1
" <b>Isis Valuation</b> "	20.2
" <b>Management Committee</b> "	7.2.1
" <b>Presiding Justice</b> "	20.2
" <b>Purchase Price</b> "	20.2
" <b>R&amp;D Committee</b> "	7.2.2
" <b>Relevant Event</b> "	21.2
" <b>Research Funding</b> "	9.3
" <b>Transfer</b> "	17.1

1.3 Words importing the singular shall include the plural and vice versa.

1.4 Unless the context otherwise requires, reference to a recital, article, paragraph, provision, clause or schedule is to a recital, article, paragraph, provision, clause or schedule of or to this Agreement.

1.5 Reference to a statute or statutory provision includes a reference to it as from time to time amended, extended or re-enacted.

1.6 The headings in this Agreement are inserted for convenience only and do not affect its construction.

1.7 Unless the context or subject otherwise requires, references to words in one gender include references to the other genders.

1.8 Capitalized terms used but not defined herein shall have the meanings ascribed in the Transaction Documents, if defined therein.

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## CLAUSE 2

### ORASENSE'S BUSINESS

2.1 The primary objectives of Orasense is to carry on the business of the development, testing, registration, Commercialization and licensing of the Product and the Development Product in the Territory and to achieve the objectives set out in this Agreement and the License Agreements. The focus of the collaborative venture will be to develop the Oral Platform and Development Candidate using the Elan Intellectual Property, the Isis Intellectual Property and the Orasense Collaboration Intellectual Property to agreed-upon specifications and timelines and to Commercialize a Product and Development Product.

2.2 Except as the Participants otherwise agree in writing and except as may be provided in this Agreement or the License Agreements, Isis and Orasense shall exercise their respective powers in relation to Orasense so as to ensure that the Business is carried on in a proper and prudent manner. Elan shall fully cooperate with Orasense and Isis in this regard through the end of the Research Term, and thereafter, at Elan's option and discretion.

2.3 Each of Isis and Orasense shall use all commercially reasonable and proper means at its disposal and within its power to maintain, extend and improve the Business of Orasense, within the limits of this Agreement, and to further the reputation and interests of Orasense.

2.4 The central management and control of Orasense shall be exercised in Bermuda and shall be vested in the Directors and such Persons as they may delegate the exercise of their powers in accordance with the Orasense Memorandum of Association and Bye-Laws. The Participants shall use their best endeavors to ensure that to the extent required pursuant to the laws of Bermuda, and to ensure the sole residence of Orasense in Bermuda, all meetings of the Directors are held in Bermuda or other jurisdictions outside the United States and generally to ensure that Orasense is treated as resident for taxation purposes in Bermuda.

### CLAUSE 3

#### REPRESENTATIONS AND WARRANTIES

3.1 **Representations and Warranties of Orasense:** Orasense hereby represents and warrants to each of the Stockholders as follows, as of the Original Effective Date:

3.1.1 **Organization:** Orasense is an exempted company duly organized, validly existing and in good standing under the laws of Bermuda, and has all the requisite corporate power and authority to own and lease its properties, to carry on its business as presently conducted and as proposed to be conducted, to execute this Agreement, which has been duly authorized and is enforceable against Orasense in accordance with its terms, and to carry out the transactions contemplated hereby.

3.1.3 **Authorization:** The execution, delivery and performance by Orasense of this Agreement, including the issuance of the Shares, have been duly authorized by all requisite corporate actions; this Agreement has been duly executed and delivered by Orasense and is the valid and binding obligation of Orasense, enforceable against it in accordance with its terms, except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and by general equity principles and limitations on the availability of equitable relief, including specific performance. The Shares, when issued as contemplated hereby, will be validly issued and outstanding, fully paid and non-assessable and not subject to preemptive or any other similar rights of the Stockholders or others.

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3.1.4 **No Conflicts:** The execution, delivery and performance by Orasense of this Agreement, the issuance, sale and delivery of the Shares, and compliance with the provisions hereof by Orasense, will not:

(i) violate any provision of applicable law, statute, rule or regulation applicable to Orasense or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to Orasense or any of its properties or assets;

(ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under its charter or organizational documents or any material contract to which Orasense is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have a material adverse effect on Orasense; or

(iii) result in the creation of, any Encumbrance upon any of the properties or assets of Orasense, except as contemplated by the Transaction Documents.

3.1.5 **Approvals:** As of the date hereof, no permit, authorization, consent or approval of or by, or any notification of or filing with, any Person is required in connection with the execution, delivery or performance of this Agreement by Orasense. Orasense has full authority to conduct its business as contemplated in the Research Plan and the Transaction Documents.

3.2 **Representations and Warranties of the Stockholders:** Each of the Stockholders hereby severally represents and warrants to Orasense as of the Original Effective Date, as follows:

3.2.1 **Organization:** Such Stockholder is a corporation duly organized and validly existing under the laws of its jurisdiction of organization and has all the requisite corporate power and authority to own and lease its respective properties, to carry on its respective business as presently conducted and as proposed to be conducted and to carry out the transactions contemplated hereby.

3.2.2 **Authority:** Such Stockholder has full corporate power and authority to enter into this Agreement and to perform its obligations hereunder, which have been duly authorized by all requisite corporate action of such Stockholder. This Agreement is the valid and binding obligation of such Stockholder, enforceable against it in accordance with its terms, except as limited by applicable bankruptcy, insolvency, reorganization, moratorium and other laws of general application affecting the enforcement of creditors' rights generally, and by general equity principles and limitations on the availability of equitable relief, including specific performance.

3.2.3 **No Conflicts:** The execution, delivery and performance by such Stockholder of this Agreement, purchase of the Shares and compliance with the provisions hereof by such Stockholder will not:

(i) violate any provision of applicable law, statute, rule or regulation known by and applicable to such Stockholder or any ruling, writ, injunction, order, judgment or decree of any court, arbitrator, administrative agency or other governmental body applicable to such Stockholder or any of its properties or assets;

(ii) conflict with or result in any breach of any of the terms, conditions or provisions of, or constitute (with notice or lapse of time or both) a default (or give rise to any right of termination, cancellation or acceleration) under the charter or organizational documents of such Stockholder or any material contract to which such Stockholder is a party, except where such violation, conflict or breach would not, individually or in the aggregate, have a material adverse effect on such Stockholder; or

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(iii) result in the creation of, any Encumbrance upon any of the properties or assets of such Stockholder, except as contemplated by the Transaction Documents.

3.2.4 **Approvals:** As of the date hereof, no material permit, authorization, consent or approval of or by, or any notification of or filing with, any Person is required in connection with the execution, delivery or performance of this Agreement by such Stockholder.

3.2.5 **Investment Representations:** Such Stockholder is capable of evaluating the merits and risks of its investment in Orasense. Such Stockholder has not been formed solely for the purpose of making this investment and such Stockholder is acquiring the Common Stock, if any, for investment for its own account, not as a nominee or agent, and not with the view to, or for resale in connection with, any distribution of any part thereof. Such Stockholder understands that the Shares have not been registered under the Securities Act or applicable state and foreign securities laws by reason of a specific exemption from the registration provisions of the Securities Act and applicable state and foreign securities laws, the availability of which depends upon, among other things, the bona fide nature of the investment intent and the accuracy of such Stockholders' representations as expressed herein. Such Stockholder understands that no public market now exists for any of the Shares and that there is no assurance that a public market will ever exist for such Shares.

3.3 **Survival:** The representations and warranties in this Clause 3 shall survive for a period of two years from and after the date hereof.

#### CLAUSE 4

##### AUTHORIZATION AND CLOSING

4.1 On the Original Effective Date, Orasense authorized the issuance to (i) EIS of 2,388 shares of Common Stock and (ii) Isis of 9,612 shares of Common Stock, issuable as provided in Clause 4.3 hereof

4.2 On the Original Effective Date, Orasense issued and sold to EIS, and EIS purchased from Orasense, upon the terms and subject to the conditions set forth herein, 2,388 shares of Common Stock for an aggregate purchase price of \$2,985,000. Orasense issued and sold to Isis, and Isis purchased from Orasense, upon the terms and conditions set forth herein, 9,612 shares of Common Stock for an aggregate purchase price of \$12,015,000.

4.3 [\*\*\*] The parties agree that they will take all action reasonably necessary, including amending the Orasense Memorandum of Association and Bye-Laws to increase the number of shares reserved for issuance by Orasense, to ensure the issuance of the Stock contemplated by this Section 4.3.

4.4 A closing shall take place in six month intervals (each, a "**Closing**") commencing [\*\*\*] and will be held at the offices of Isis at 2292 Faraday Avenue, Carlsbad, California 92008 or such other place if any, as the Parties may agree.

4.5 At each Closing,

4.5.1 Orasense shall issue and sell to the Stockholders the applicable number of shares, calculated pursuant to Section 4.3 above.

4.5.2 The Parties shall execute and deliver to each other, as applicable, certificates in respect of the Common Stock described above and any other certificates, resolutions or documents which the Parties shall reasonably require.

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4.6 **Exemption from Registration:**

The Shares will be issued under an exemption or exemptions from registration under the Securities Act. Accordingly, the certificates evidencing the Shares shall, upon issuance, contain the following legend:

**THE SECURITIES REPRESENTED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT UNDER ANY CIRCUMSTANCES BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF WITHOUT AN EFFECTIVE REGISTRATION STATEMENT FOR SUCH SECURITIES UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND ANY APPLICABLE STATE SECURITIES LAWS OR AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY THAT REGISTRATION IS NOT REQUIRED UNDER SUCH ACT OR APPLICABLE STATE SECURITIES LAWS.**

**THE TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS ALSO SUBJECT TO THE RESTRICTIONS CONTAINED IN THAT CERTAIN AMENDED AND RESTATED SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT, DATED OCTOBER 14, 2002, BY AND AMONG ELAN CORPORATION, PLC, ELAN INTERNATIONAL SERVICES, INC., ISIS PHARMACEUTICALS, INC. AND ORASENSE LTD.**

CLAUSE 5

DELETED

CLAUSE 6

NON-COMPETITION

6.1 From the Original Effective Date and through [\*\*\*], the Parties agree to be bound by the provisions of Clause 11 of the Elan License Agreement and the provisions of Clause 11 of the Isis License Agreement, which set forth the agreement between the parties thereto in relation to the non-competition obligations of Elan and Isis, respectively.

CLAUSE 7

7.1. **Directors:**

The Board of Directors of Orasense shall be composed of four Directors. Prior to an Elan Minority Interest, Isis shall have the right to nominate three directors of Orasense ("**Isis Directors**") and EIS shall have the right to nominate one Director of Orasense ("**EIS Director**"); provided that one such director is a resident of Bermuda. Isis may appoint one of the Isis Directors to be the chairman of Orasense. Each Participant agrees to vote its shares of Common Stock in favor of the election of the nominees of the other Participant to the Board of Directors.

7.1.1 If the chairman is unable to attend any meeting of the Board, the Isis Directors shall be entitled to appoint another Director to act as chairman in his place at the meeting.

7.1.2 If EIS removes the EIS Director, or Isis removes any of the Isis Directors, EIS or Isis, as the case may be, shall indemnify the other Stockholder against any claim by such removed Director arising from such removal.

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7.1.3 Prior to an Elan Minority Interest, the Directors shall meet not less than three times in each Financial Year and all Directors' meetings shall be held in Bermuda to the extent required pursuant to the laws of Bermuda or to ensure the sole residence of Orasense in Bermuda.

7.1.4 Prior to an Elan Minority Interest, at any such meeting, the presence of the EIS Director and one of the Isis Directors shall be required to constitute a quorum and after an Elan Minority Interest, a majority of the then acting directors will be required to constitute a quorum. Subject to Clause 18 hereof, the affirmative vote of a majority of the Directors present at a meeting at which such a quorum is present shall constitute an action of the Directors. In the event of any meeting being inquorate, the meeting shall be adjourned for a period of seven days. A notice shall be sent to the EIS Director and the Isis Directors specifying the date, time and place where such adjourned meeting is to be held and reconvened.

7.1.5 In the event of an Elan Minority Interest, each of Isis, and EIS shall cause the board of Directors of Orasense to be reconfigured so that all of the Directors are designated by Isis and EIS will lose its right to nominate any Directors of Orasense.

7.1.6 In case of an equality of votes at a meeting of the board of Directors of Orasense, the chairman of Orasense shall not be entitled to a second or casting vote. In the event of continued deadlock, the board of Directors shall resolve the deadlock pursuant to the provisions set forth in Clause 19.

7.2 **Management and R&D Committees:**

7.2.1 On or about the Original Effective Date, the Directors appointed a management committee (the "**Management Committee**") to perform certain operational functions, such delegation to be consistent with the Directors' right to delegate powers pursuant to the Orasense Memorandum of Association of Bye-Laws. As of the Effective Date, the Management Committee consists of four members, two of whom will be nominated by EIS and two of whom will be nominated by Isis, and each of whom shall be entitled to one vote. In the event of a Failure to Fund at any time after the end of the Research Term, EIS will lose its right to nominate members of the Management Committee and Isis will be able to nominate all the members of the Management Committee, and each member will be entitled to one vote. The affirmative vote of at least 3 members of the Management Committee will constitute an action of the Management Committee.

7.2.2 On or about the Original Effective Date, the Management Committee appointed a research and development committee (the "**R&D Committee**") which is comprised of four members, two of whom were nominated by Elan and two of whom were nominated by Isis, and each of whom have one vote. In the event of a Failure to Fund at any time after the end of the Research Term, EIS will lose its right to nominate members of R&D Committee and Isis will be able to nominate all the members of the R&D Committee, and each member will be entitled to one vote. The affirmative vote of at least 3 members of the R&D Committee will constitute an action of the R&D Committee.

7.2.3 The Management Committee's responsibilities include, inter alia, devising, implementing and reviewing strategy for the business and operations of Orasense, and in particular, devising Orasense's strategy for research and development and to monitor and supervise the implementation of Orasense's strategy for research and development.

7.2.4 The R&D Committee is responsible for:

7.2.4.1 establishing a joint Project team consisting of an equal number of team members from Elan and Isis, including one Project leader from each of Elan and Isis, except after an Elan Minority Interest the joint project team will consist of all Isis team members; and

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7.2.4.2 implementing such portion of the Research Plan that relates to the Project, as approved by the Management Committee.

7.2.5 In the event of any dispute amongst the R&D Committee, the R&D Committee shall refer such dispute to the Management Committee whose decision on the dispute shall be binding on the R&D Committee. If the Management Committee cannot resolve the matter, the dispute will be referred to the President of Elan and the Chief Executive Officer of Isis pursuant to Clause 19 hereof.

7.2.6 On not more than [\*\*\*] times in each Financial Year, Elan and Isis shall permit Orasense or its duly authorized representative on reasonable notice and at any reasonable time during normal business hours to have access to inspect and audit the accounts and records of Elan or Isis and any other book, record, voucher, receipt or invoice relating to the calculation or the cost of the Research Plan and to the accuracy of the reports which accompanied them. Any such inspection of Elan's or Isis's records, as the case may be, shall be at the expense of Orasense, except that if such inspection reveals an overpayment in the amount paid to Elan or Isis, as the case may be, for the Research Plan hereunder in any Financial Year of [\*\*\*] or more of the amount due to Elan or Isis, as the case may be, then the expense of such inspection shall be borne solely by Elan or Isis, as the case may be, instead of by Orasense. Any surplus over the sum properly payable by Orasense to Elan or Isis, as the case may be, shall be paid promptly by Elan or Isis, as the case

may be, to Orasense. If such inspection reveals a deficit in the amount of the sum properly payable to Elan or Isis, as the case may be, by Orasense, Orasense shall pay the deficit to Elan or Isis, as the case may be.

## CLAUSE 8

### THE RESEARCH PLAN AND REVIEWS

8.1 The Directors have met and agreed upon the Research Plan, including the applicable budget. Except for material modifications to the Research Plan, no additional approval is needed from the Directors to carry out the Research Plan.

8.2 The Participants agree that the Management Committee shall submit to the Directors on February 15th, May 15th, August 15th, and November 15th or as soon as reasonably practicable thereafter in each Financial Year a report on the performance of the Business and research and development activities of Orasense, and the Directors shall hold such meeting as may be necessary to review the performance of Orasense against the Research Plan for the relevant year.

## CLAUSE 9

### RESEARCH AND DEVELOPMENT WORK; FUNDING

9.1 Orasense will diligently pursue the research, development and Commercialization of the Elan Intellectual Property, Isis Intellectual Property and Orasense Intellectual Property. During the Research Term, such work shall be agreed to and conducted by Elan and/or Isis under contract with Orasense as provided in the Research Plan. At the end of the Research Term, Isis and Elan may decide by mutual written agreement to extend the Research Term and adopt a corresponding Research Plan.

9.2 During the Research Term, Elan and Isis shall provide reasonable research and development services as may be reasonably required by Orasense in accordance with the provisions in the License Agreements. Orasense shall pay Isis and Elan for any research and development work carried out by each of Isis and Elan on behalf of Orasense at the end of each month, and any extension thereto, subject to the proper vouching of research and development work and expenses. An invoice shall be issued to Orasense by Isis or Elan, as applicable, by the 15<sup>th</sup> day of the month following the month in

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which work was performed. The payments by Orasense to Isis or Elan, as the case may be, shall be at the rates prescribed in the respective License Agreement. Research and development activities that are outsourced to third party providers shall be charged to Orasense at fully burdened actual costs.

9.3 Isis and EIS agree to fund the Research Plan through the end of the Research Term pursuant to the budget attached to the Research Plan (the "**Research Funding**") by contributing cash to Orasense, such funding to be provided on a pro rata basis in accordance with their respective ownership interests in Orasense; [\*\*\*]

9.4 The Research Funding will be provided by EIS and Isis at such times as shall be necessary under the Research Plan, as shall be reasonably determined in good faith by the decision of the Directors.

9.5 At the end of the Research Term, EIS will have [\*\*\*] days to notify Orasense in writing whether EIS wishes to continue funding the Research Plan. If EIS fails to notify Orasense in writing within such [\*\*\*]-day period of its decision to continue funding, then, notwithstanding anything contained herein to the contrary, EIS will no longer be obligated to fund the Research Plan nor shall Elan be obligated to provide employees, services or other assistance to Orasense and a "Failure to Fund" will be deemed to have occurred. In the event of a Failure to Fund, Isis may continue funding the Research Plan and will receive Shares as provided in Section 4 of this Agreement.

9.6 Reference is made to Sections 2.4, 7.2.1, 7.2.2, 10.3, 16.1 and 18.2 of this Agreement and Section 12.5 of the Isis License Agreement with respect to certain rights that will terminate after a Failure to Fund.

## CLAUSE 10

### INTELLECTUAL PROPERTY RIGHTS

10.1 Title and all other ownership rights, including patent rights, relating to the Orasense Intellectual Property shall belong to Orasense. Title and all other ownership rights, including patent rights, relating to the Isis Intellectual Property shall belong to Isis. Title and all other ownership rights, including patent rights, relating to the Elan Intellectual Property shall belong to Elan. Otherwise, title and all other ownership rights will belong to the Party inventing an invention.

10.2 Prior to a Failure to Fund, the Participants shall discuss in good faith all material issues relating to filing, prosecution and maintenance of Patents within the Orasense Intellectual Property insofar as such Patents are of relevance to the Field and any patentable inventions discovered by Elan, Isis or Orasense that relate to the Field and any patentable improvements thereto. Subject to mutual agreement to the contrary by Isis and Elan the following provisions shall apply:

10.2.1 Orasense, shall (i) file and prosecute patent applications on patentable inventions and discoveries within the Orasense Collaboration Intellectual Property; (ii) defend all such applications against third party oppositions; and (iii) maintain in force any issued letters patent within the Orasense Intellectual Property (including any patents that issue on patentable inventions and discoveries within the Orasense Intellectual Property). Orasense shall control such filing, prosecution, defense and maintenance.

10.2.2 Orasense, Elan and Isis shall promptly inform each other in writing of any alleged infringement of any Patents within the Elan Intellectual Property, the Isis Intellectual Property or the Orasense Collaboration Intellectual Property or any alleged misappropriation of trade secrets within the Elan Intellectual Property, the Isis Intellectual Property or the Orasense Collaboration Intellectual Property by a third party of which it becomes aware and provide the Participants and Orasense with any available evidence of such infringement or misappropriation insofar as such infringements or misappropriation relate solely to the Field.

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10.3 Orasense shall have the first right but not the obligation to bring suit or otherwise take action against any alleged infringement of the Orasense Intellectual Property or alleged misappropriation of the Orasense Intellectual Property. If any such alleged infringement or misappropriation occurs that gives rise to a cause of action both inside and outside the Field, Orasense, in consultation with the Participants, shall determine the cause of action to be taken. In the event that Orasense takes such action, Orasense shall do so at its own cost and expense and all damages and monetary award recovered in or with respect to such action shall be the property of Orasense. Orasense shall keep Elan and Isis informed of any action in a timely manner so as to enable Isis and Elan to provide input in any such action and Orasense shall reasonably take into consideration any such input. At Orasense's request, the Participants shall cooperate with any such action at Orasense's cost and expense.

10.4 In the event that Orasense does not bring suit or otherwise take action against all infringement of the Orasense Intellectual Property or misappropriation of the Orasense Intellectual Property, then (i) if only one Participant determines to pursue such suit or take such action at its own cost and expense, it shall be entitled to all damages and monetary award recovered in or with respect to such action and (ii) if the Participants pursue such suit or action outside of Orasense, they shall negotiate in good faith an appropriate allocation of costs, expenses and recovery amounts.

10.5 In the event that a claim is, or proceedings are, brought against Orasense by a third party alleging that the sale, distribution or use of a Product in the Territory or use of the Orasense Intellectual Property or the Isis Intellectual Property, as the case may be, infringes the intellectual property rights of such party, Orasense shall promptly advise the other Participants of such threat or suit.

10.6 Orasense and Isis and any of their respective sublicensees shall indemnify, defend and hold harmless Elan and its Affiliates, and each of Elan's and its Affiliates' respective employees, agents, partners, officers and directors (each an "**Indemnified Party**") against all actions, losses, claims, demands, damages, costs and liabilities (including reasonable attorneys fees) relating directly or indirectly to all such claims or proceedings referred to in Clause 10.4 above, provided that Elan shall not acknowledge to the third party or to any other person the validity of any claims of such a third party, and shall not compromise or settle any claim or proceedings relating thereto without the prior written consent to Orasense, not to be unreasonably withheld or delayed. At its option, Elan or Isis, as the case may be, may elect to take over the conduct of such proceedings from Orasense provided that Orasense's indemnification obligations shall continue; the costs of defending such claim shall be borne by Elan or Isis, as the case may be and such Participant shall not compromise or settle any such claim or proceeding without the prior written consent of Orasense, such consent not to be unreasonably withheld or delayed.

10.7 Orasense shall not encumber any of its rights under the Licenses (except as permitted therein and in Section 12.2 hereof) or the Orasense Intellectual Property without the prior written consent of Elan and Isis; provided that after a Failure to Fund, Elan's consent rights with respect to the Isis License and Orasense Post-Collaboration Property will no longer be required. Orasense shall not be permitted to assign or sublicense any of its rights under the Licenses (except as expressly provided under the Elan License Agreement and Isis License Agreement) or the Orasense Intellectual Property without the prior written consent of Elan and Isis, respectively, which may be withheld in Elan's or Isis' sole discretion, as the case may be; provided that after a Failure to Fund, Elan's consent rights with respect to the Isis License or Orasense Post-Collaboration Intellectual Property will no longer be required.

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## CLAUSE 11

### UNBLOCKING LICENSES

11.1 Isis and its Affiliates shall secure the right to sublicense to Elan any Isis Blocking Invention made by Isis, Orasense or any of their respective Affiliates and/or sublicensees or any Independent Third Party under contract with Isis, Orasense or any of their respective Affiliates and/or sublicensees. Isis hereby grants to Elan a royalty free, world-wide, irrevocable, [\*\*\*] license, including the right to grant sublicenses, to research, develop, make and have made, offer for sale, sell, import and export products incorporating the Isis Blocking [\*\*\*] to practice the Elan Intellectual Property and/or Orasense Intellectual Property to the extent same could not otherwise be practiced without first obtaining a license to such Isis Blocking Invention.

11.2 Orasense and its Affiliates shall secure the right to sublicense to Elan any Orasense Blocking Invention made by Isis, Orasense or any of their respective Affiliates and/or sublicensees or any Independent Third Party under contract with Isis, Orasense or any of their respective Affiliates and/or sublicensees. Isis hereby grants to Elan a royalty free, world-wide, irrevocable, [\*\*\*] license, including the right to grant sublicenses, to research, develop, make and have made, offer for sale, sell, import and export products incorporating the Isis Blocking Inventions [\*\*\*] to practice the Elan Intellectual Property and/or Orasense Intellectual Property to the extent same could not otherwise be practiced without first obtaining a license to such Isis Blocking Invention.

11.3 Orasense and Isis and each of their respective Affiliates will [\*\*\*] efforts to exclude or, where applicable, minimize royalty or other compensation obligations in respect of any Isis Blocking Invention and/or Orasense Blocking Invention, as the case may be. Elan will be responsible for the payment of such royalty or other compensation obligations triggered by Elan's practice and use of the Isis Blocking Invention and/or Orasense Isis Blocking Invention, as the case may be, solely to the extent a royalty or other compensation obligation to Independent Third Parties are payable with respect to Elan's use of an Isis Blocking Invention and/or Orasense Blocking Invention, as the case may be; *provided, however*, that any royalty or other compensation obligations payable by Elan to such Independent Third Parties under such license shall be substantially similar to the royalty obligations or other compensation obligations payable by Isis and/or Orasense in connection with any license to an invention or discovery and Patents that may issue thereon that would prevent Isis and or Orasense from practicing the Elan Intellectual Property and/or the Orasense Collaboration Intellectual Property licensed to such Independent Third Party, but for such license.

## CLAUSE 12

### COMMERCIALIZATION

12.1 The Participants shall, during the Research Term, assist Orasense in diligently pursuing the research, development, prosecution and commercialization of Products in accordance with the Research Plan.

12.2 During and following the Research Term, Isis as an agent for Orasense, may negotiate and execute with Independent Third parties regarding a license and collaboration agreement for developing and Commercializing the Development Candidate. By executing this Agreement, Elan, and its nominees on the Board and its nominees on the Management Committee authorize Isis and Orasense to conduct such negotiation and to execute any agreement that may arise therefrom.

12.3 In the event an Independent Third Party shall propose to Orasense the development of Third Party Products, the Management Committee, by unanimous decision, shall determine whether or not to develop any such Third Party Product. Orasense shall be responsible for negotiating with any

Independent Third Parties commercially reasonable terms (e.g., royalties, milestones, development fees, manufacturing rights) for developing and licensing Third Party Products.

**CLAUSE 13**

**MANUFACTURING**

13.1 Isis will notify Elan in writing of Isis' good faith intention to manufacture or have manufactured an Oligonucleotide Drug incorporating any Elan Intellectual Property. Elan will have [\*\*\*] from the receipt of such notice to notify Isis in writing whether or not Elan wishes to negotiate with Isis regarding the manufacture of the Oligonucleotide Drug. If Elan fails to respond to Isis' notice within the [\*\*\*] or if Elan declines in writing to exercise its right of first negotiation, then, Isis will be free to manufacture and supply (either on its own or with a third party) the Oligonucleotide Drug. If Elan wishes to manufacture the Oligonucleotide Drug incorporating any Elan Intellectual Property, the parties will negotiate in good faith the terms of a manufacturing agreement. If despite good faith negotiations, Elan and Isis do not reach agreement within [\*\*\*] from Elan's exercise of its right of first negotiation, then Isis will be free to manufacture and supply (either on its own or with a third party) the Oligonucleotide Drug.

**CLAUSE 14**

**TECHNICAL SERVICES AND ASSISTANCE**

14.1 Whenever commercially and technically feasible, Orasense shall contract with Isis or Elan, as the case may be, to perform such other services as Orasense may require, other than those specifically dealt with hereunder or in the License Agreements. In determining which Party should provide such services, the Management Committee shall take into account the respective infrastructure, capabilities and experience of Elan and Isis.

14.2 The Parties agree that each Party shall effect and maintain comprehensive general liability insurance under industry standard insurance policies in respect of all clinical trials and other activities performed by them on behalf of Orasense.

14.3 If Elan or Isis so requires, Isis or Elan, as the case may be, shall receive, at times and for periods mutually acceptable to the Parties, employees of the other Party (such employees to be acceptable to the receiving Party in the matter of qualification and competence) for instruction in respect of the Elan Intellectual Property or the Isis Intellectual Property, as the case may be, as necessary to further the Research Plan.

14.4 The employees received by Elan or Isis, as the case may be, shall be subject to obligations of confidentiality no less stringent than those set out in Clause 22 and such employees shall observe the rules, regulations and systems adopted by the Party receiving the said employees for its own employees or visitors.

**CLAUSE 15**

**AUDITORS, BANKERS, REGISTERED OFFICE,  
ACCOUNTING REFERENCE DATE; SECRETARY; COUNSEL**

Unless otherwise agreed by the Stockholders and save as may be provided to the contrary herein:

15.1 the auditors of Orasense shall be Ernst & Young;

15.2 the bankers of Orasense shall be Bank of Bermuda or such other bank as may be agreed by the Directors from time to time;

15.3 the accounting reference date of Orasense shall be December 31st in each Financial Year; and

15.4 the secretary of Orasense shall be Diana Martin or such other Person as may be appointed by the Directors from time to time.

**CLAUSE 16**

**REGULATORY**

16.1 Orasense shall keep the other Parties promptly and fully advised of Orasense's regulatory activities, progress and procedures; provided, however, that Elan's rights hereunder will terminate after a Failure to Fund, except as is otherwise set forth under the Elan License Agreement. Orasense shall inform the other Parties of any dealings it shall have with a Regulatory Authority, and shall furnish the other Parties with copies of all correspondence relating to the Products. The Parties shall collaborate to obtain any required regulatory approval of the Regulatory Authority to market the Products.

16.2 Orasense shall, at its own cost, file, prosecute and maintain any and all Regulatory Applications for the Products in the Territory in accordance with the Research Plan.

16.3 Any and all Regulatory Approvals obtained hereunder for any Product shall remain the property of Orasense, provided that Orasense shall allow Elan and Isis access thereto to enable Elan and Isis to fulfill their respective obligations and exercise their respective rights under this Agreement. Orasense shall maintain such Regulatory Approvals at its own cost.

16.4 It is hereby acknowledged that there are inherent uncertainties involved in the registration of pharmaceutical products with the Regulatory Authorities insofar as obtaining approval is concerned and such uncertainties form part of the business risk involved in undertaking the form of commercial collaboration as set forth in this Agreement. Therefore, except for liabilities resulting from failure to use reasonable efforts, none of Elan, EIS or Isis shall have any liability to Orasense solely as a result of any failure of a Product to achieve the approval of any Regulatory Authority.

## CLAUSE 17

### TRANSFERS OF SHARES

#### 17.1 **General:**

No Stockholder shall, directly or indirectly, sell or otherwise transfer (each, a "**Transfer**") any Shares held by it except in accordance with this Agreement. Orasense shall not, and shall not permit any transfer agent or registrar for any Shares to, transfer upon the books of Orasense any Shares from any Stockholder to any transferee, in any manner, except in accordance with this Agreement, and any purported transfer not in compliance with this Agreement shall be void.

## CLAUSE 18

### MATTERS REQUIRING PARTICIPANTS' APPROVAL

18.1 In consideration of Isis and Elan agreeing to enter into the License Agreements, the Parties hereby agree that Orasense shall not without the prior approval of the EIS Director and at least two of the Isis Directors:

18.1.1. issue any unissued Shares or create or issue any new shares, except as expressly permitted by the Orasense Bylaws and as contemplated under this Agreement;

18.1.2. alter any rights attaching to any class of share in the capital of Orasense or alter the Orasense Memorandum of Association and Bye-Laws;

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18.1.3. consolidate, sub-divide or convert any of Orasense's share capital or in any way alter the rights attaching thereto;

18.1.4. dispose of Orasense or of any shares in Orasense;

18.1.5. do or permit or suffer to be done any act or thing whereby Orasense may be wound up (whether voluntarily or compulsorily), save as otherwise expressly provided for in this Agreement;

18.1.6. enter into any material contract or transaction except in the ordinary and proper course of the Business on arm's length terms, or as contemplated by the Research Plan;

18.1.7. alter the number of Directors;

18.1.8. change the domicile of Orasense from Bermuda;

18.1.9. register any stock of Orasense with any governmental authority for public trading in any securities market;

18.1.10. pay dividends or distributions in respect of, or redeem or repurchase, the equity of Orasense; or

18.1.11. adopt or register or use any trade name, trademark or service mark on behalf of Orasense.

18.2 In the event of a Failure to Fund, items 18.1.4, 18.1.6, 18.1.9 and 18.1.10 will be of no further force and effect. In the event of an Elan Minority Interest, all of the rights under Section 18.1 will be of no further force or effect.

## CLAUSE 19

### DISPUTES

19.1 Should any dispute or difference arise between Elan and Isis, or between Elan or Isis and Orasense, during the period that this Agreement is in force, other than a dispute or difference relating to (i) the interpretation of any provision of this Agreement, (ii) the interpretation or application of law, or (iii) the ownership of any intellectual property, then any Party may forthwith give notice to the other Parties that it wishes such dispute or difference to be referred to the Chief Executive Officer of Isis and the President of Elan.

19.2 In any event of a notice being served in accordance with Clause 19.1, each of the Participants shall within 14 days of the service of such notice prepare and circulate to the Chief Executive Officer of Isis and the President of Elan a memorandum or other form of statement setting out its position on the matter in dispute and its reasons for adopting that position. Each memorandum or statement shall be considered by the Chief Executive Officer of Isis and the President of Elan who shall endeavor to resolve the dispute. If the chief executive officers of the Participants agree upon a resolution or disposition of the matter, they shall each sign a statement which sets out the terms of their agreement. The Participants agree that they shall exercise the voting rights and other powers available to them in relation to Orasense to procure that the agreed terms are fully and promptly carried into effect.

## CLAUSE 20

### BUYOUT



20.1 After Elan's ownership interest in Orasense falls below [\*\*\*] Isis shall have the right to purchase the shares of Orasense Common Stock held by Elan (the "**Buyout Option**"), or its Affiliates

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for the stock's then fair market value, as determined by senior officers of Elan and Isis. Isis will notify Elan in writing of its decision to purchase such shares.

20.2 In the event that the Participants do not agree upon a purchase price for the Shares within [\*\*\*] Business Days following the receipt by Isis of written notice from Elan pursuant to Clause 20.1 above, the Participants shall jointly select a nationally recognized investment banking firm as arbitrator to make such determination. In the event the Participants do not agree upon the selection of such investment banking firm, Elan may contact the presiding justice of the Supreme Court of the State of New York sitting in the City, County, and State of New York (the "**Presiding Justice**") and request that an independent US-based nationally recognized investment banking firm which is knowledgeable of the pharmaceutical/biotechnology industry be appointed within 10 Business Days. The Presiding Justice shall endeavor to select an investment banking firm as arbitrator which is technically knowledgeable in the pharmaceutical/biotechnology industry (and which directly and through its Affiliates, has no business relationship with, or shareholding in, either of the Participants). Promptly upon being notified of the arbitrator's appointment, the Participants shall submit to the arbitrator details of their assessment [\*\*\*] together with such information as they think necessary to validate their assessment. The arbitrator shall notify Isis of the [\*\*\*] and shall notify Elan of [\*\*\*] The Participants shall then be entitled to make further submissions to the arbitrator within five Business Days explaining why the proposed valuations, as the case may be, are unjustified. The arbitrator shall thereafter meet with Isis and Elan and shall thereafter choose either [\*\*\*] on the basis of [\*\*\*] The arbitrator shall use its best efforts to determine the [\*\*\*] within 30 Business Days of his appointment. The Participants shall bear the costs of the arbitrator equally provided that the arbitrator may, in its discretion, allocate all or a portion of such costs to one Party. Any decision of the arbitrator shall be final and binding.

20.3 Isis shall purchase the Shares beneficially owned by Elan by delivery of the Purchase Price in cash no later than the 15th Business Day following determination of the Purchase Price by the arbitrator.

20.4 The Shares so transferred shall be sold by Elan with effect from the date of such transfer free from any lien, charge or encumbrance, but with all rights and restrictions attaching thereto.

20.7 If Isis exercises the Buyout Option, the provisions of Clauses 1, 3, 10.1, 10.3, 10.4, 10.5, 10.6, 11, 19, 20.7, 21, 22, 23 and 24 shall survive the termination of this Agreement under this Clause 20.7; all other terms and provisions of this Agreement shall cease to have effect and be null and void.

## CLAUSE 21

### TERMINATION

21.1 This Agreement shall govern the operation and existence of Orasense until (i) terminated by written agreement of all Parties hereto or (ii) otherwise terminated in accordance with this Clause 21.

21.2 For the purpose of this Clause 21, a "**Relevant Event**" is committed or suffered by a Participant if:

21.2.1 it commits a material breach of its obligations under this Agreement or the applicable License, which breach remains uncured [\*\*\*] after written notice thereof; provided, however, that (x) if the breaching Participant has proposed a course of action to rectify the breach and is acting in good faith to rectify same but has not cured the breach by the [\*\*\*], such period shall be extended by such period as is reasonably necessary to permit the breach to be rectified and (y) if a default involves a good faith dispute regarding the amount of any required payment, provided any undisputed amount is paid, such default shall be stayed and the remainder may be withheld for a reasonable period during which a good faith resolution of the amount owed is being pursued;

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21.2.2 a distress, execution, sequestration or other process is levied or enforced upon or sued out against a material part of its property which is not discharged or challenged within 30 days;

21.2.3 it is unable to pay its debts in the normal course of business;

21.2.4 it ceases wholly or substantially to carry on its business, otherwise than for the purpose of a reconstruction or amalgamation, without the prior written consent of the other Participant (such consent not to be unreasonably withheld);

21.2.5 the appointment of a liquidator, receiver, administrator, examiner, trustee or similar officer of such Participant or over all or substantially all of its assets under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland;

21.2.6 an application or petition for bankruptcy, corporate re-organization, composition, administration, examination, arrangement or any other procedure similar to any of the foregoing under the law of any applicable jurisdiction, including without limitation, the United States of America, Bermuda or Ireland, is filed, and is not discharged within 60 days, or a Participant applies for or consents to the appointment of a receiver, administrator, examiner or similar officer of it or of all or a material part of its assets, rights or revenues or the assets and/or the business of a Participant are for any reason seized, confiscated or condemned.

21.3 If either Participant commits a Relevant Event, the other Stockholder shall have in addition to all other legal and equitable rights and remedies hereunder, the right to terminate this Agreement upon 30 days' written notice.

21.4 In the event of a termination of the Elan License Agreement and/or the Isis License Agreement, both parties will negotiate in good faith to determine whether this Agreement should be terminated and if so, which provisions should survive termination.

21.5 The provisions of Clauses 1, 3, 10.1, 10.3, 10.4, 10.5, 10.6, 11, 19, 20.7, 21, 22, 23 and 24 shall survive the termination of this Agreement under Clause 21.3 or by mutual consent pursuant to Clause 21.1 in accordance with their terms; all other terms and provisions of this Agreement shall cease to have effect and be null and void upon the termination of this Agreement under Clause 21.3 or by mutual consent pursuant to Clause 21.1.

## CLAUSE 22

### CONFIDENTIALITY

22.1 The Parties acknowledge that it may be necessary, from time to time, to disclose to each other confidential and proprietary information, including without limitation, Patents, inventions, works of authorship, trade secrets, specifications, designs, data, Know-How and other information relating to the Field, the Products, Elan Intellectual Property, Isis Intellectual Property and Orasense Intellectual Property, as the case may be, processes, services and business of the disclosing Party. The foregoing shall be referred to collectively as "**Confidential Information**". Any Confidential Information revealed by a Party to another Party shall be used by the receiving Party exclusively for the purposes of fulfilling the receiving Party's obligations under this Agreement and the Development Agreement and for no other purpose.

22.2 Each Party agrees to disclose Confidential Information of another Party only to those employees, representatives and agents requiring knowledge thereof in connection with their duties directly related to the fulfilling of the Party's obligations under this Agreement. Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving

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Confidential Information. Each Party agrees that it will exercise the same degree of care, but in no event less than a reasonable degree and protection to preserve the proprietary and confidential nature of the Confidential Information disclosed by a Party, as the receiving Party would exercise to preserve its own proprietary and confidential information. Each Party agrees that it will, upon request of a Party, return all documents and any copies thereof containing Confidential Information belonging to or disclosed by, such Party.

22.3 Notwithstanding the above, each Party may use or disclose Confidential Information disclosed to it by another party to the extent such use or disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, complying with patent applications, complying with applicable governmental regulations or otherwise submitting information to tax or other governmental authorities, conducting clinical trials, or making a permitted sub-license or otherwise exercising its rights hereunder, provided that if a Party is required to make any such disclosure of the other Party's Confidential Information, other than pursuant to a confidentiality agreement, such Party shall inform the recipient of the terms and provisions of this Agreement and their duties hereunder and to obtain their consent hereto as a condition of receiving Confidential Information.

22.4 Any breach of this Clause 22 by any of the Persons informed by one of the Parties is considered a breach by the Party itself.

22.5 Confidential Information shall not be deemed to include:

22.5.1 information that is generally available to the public;

22.5.2 information which is made public by the disclosing Party;

22.5.3 information which is independently developed by a Party as evidenced by such Party's written records, without the aid, application or use of the disclosing Party's Confidential Information;

22.5.4 information that is published or otherwise becomes part of the public domain without any disclosure by a Party, or on the part of a Party's directors, officers, agents, representatives or employees;

22.5.6 information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis;

22.5.7 information that becomes available to a Party on a non-confidential basis, whether directly or indirectly, from a source other than a Party, which source did not acquire this information on a confidential basis;

22.5.8 information which the receiving Party is required to disclose pursuant to;

22.5.8.1 a valid order of a court or other governmental body or any political subdivision thereof or otherwise required by law; or

22.5.8.2 any other requirement of law;

provided that if the receiving Party becomes legally required to disclose any Confidential Information, the receiving Party shall give the disclosing Party prompt notice of such fact so that the disclosing Party may obtain a protective order or other appropriate remedy concerning any such disclosure. The receiving Party shall fully cooperate with the disclosing Party in connection with the disclosing Party's efforts to obtain any such order or other remedy. If any such order or other remedy does not fully preclude disclosure, the receiving Party shall make such disclosure only to the extent that such disclosure is legally required;

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22.5.9 information which was already in the possession of the receiving Party at the time of receiving such information, as evidenced by its written records, provided such information was not previously provided to the receiving Party from a source which was under an obligation to keep such information confidential; and

22.5.10 information that is the subject of a written permission to disclose, without restriction or limitation, by the disclosing Party.

22.6 The provisions relating to confidentiality in this Clause 22 shall remain in effect during the term of this Agreement, and for a period of seven (7) years following the expiration or earlier termination of this Agreement but shall not apply to any information which a Party is required to file or otherwise disclose in accordance with requirements which are legally binding on it.

22.7 The Parties agree that the obligations of this Clause 22 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party expressly agrees that monetary damages would be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein. Accordingly, the Parties agree and acknowledge that any such violation or threatened violation will cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, any Party shall be entitled to obtain injunctive relief against the threatened breach of the provisions of this Clause 22, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with its damages and reasonable counsel fees and expenses to enforce its rights hereunder, without the necessity of proving actual or express damages.

22.8 Each of the Parties shall be entitled to provide a copy of this Agreement (and any subsequent amendments hereto) and the License Agreements to a potential third party purchaser in connection with the sale of such Party's business or assets, including without limitation, in the case of Elan, the sale of the Elan Intellectual Property; provided that the relevant third party purchaser or assignee has entered into a confidentiality agreement on terms no less protective than the terms of this Clause 22.

## CLAUSE 23

### COSTS

23.1 Each Stockholder shall bear its own legal and other costs incurred in relation to preparing and concluding this Agreement and the other Transaction Documents.

23.2 All other costs, legal fees, registration fees and other expenses relating to the transactions contemplated hereby, including the costs and expenses incurred in relation to the incorporation of Orasense, shall be borne by Orasense.

## CLAUSE 24

### GENERAL

#### 24.1 **Good Faith:**

Each of the Parties hereto undertakes with the others to do all things reasonably within its power that are necessary or desirable to give effect to the spirit and intent of this Agreement.

#### 24.2 **Further Assurance:**

At the request of any of the Parties, the other Party or Parties shall (and shall use reasonable efforts to procure that any other necessary parties shall) execute and perform all such documents, acts and things as may reasonably be required subsequent to the signing of this Agreement for assuring to or vesting in the requesting Party the full benefit of the terms hereof.

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#### 24.3 **Reliance on Representation and Warranties:**

Each of the Parties hereto hereby acknowledges that in entering into this Agreement it has not relied on any representation or warranty except as expressly set forth herein or in any document referred to herein.

#### 24.4 **Force Majeure:**

Neither Party to this Agreement shall be liable for delay in the performance of any of its obligations hereunder if such delay is caused by or results from causes beyond its reasonable control, including without limitation, acts of God, fires, strikes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances or intervention of any relevant government authority, but any such delay or failure shall be remedied by such Party as soon as practicable.

#### 24.5 **Relationship of the Parties:**

Nothing contained in this Agreement is intended or is to be construed to constitute Elan/EIS and Isis as partners, or Elan/EIS as an employee or agent of Isis, or Isis as an employee or agent of Elan/EIS.

No Party hereto shall have any express or implied right or authority to assume or create any obligations on behalf of or in the name of another Party or to bind another Party to any contract, agreement or undertaking with any third Party.

#### 24.6 **Counterparts:**

This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

#### 24.7 **Notices:**

Any notice to be given under this Agreement shall be sent in writing by registered or recorded delivery post or reputable overnight courier such as Federal Express or telecopied to:

If to Orasense at: Orasense Ltd.  
c/o Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: Ms. Lynne Parshall  
Telephone: (760) 603-2460  
Telefax: (760) 931-9639

If to Isis to: Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
Attention: Ms Lynne Parshall  
Telephone: (760) 603-2460  
Telefax: (760) 931-9639

with a copy to: Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: Grantland E. Bryce  
Telephone: 760-603-2707  
Fax: 760-268-4922

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If to Elan at: Elan Corporation, plc  
C/o Elan International Services, Ltd.  
102 St. James Court  
Flatts,  
Smiths FL04  
Bermuda  
Attention: Secretary  
Telephone: 441 292 9169  
Fax: 441 292 2224

with a copy to each of Isis, EIS and their respective counsel at the addresses indicated above;

or to such other address(es) as may from time to time be notified by any Party to the others hereunder.

Any notice sent by mail shall be deemed to have been delivered within three Business Days after dispatch or delivery to the relevant courier and any notice sent by telecopy shall be deemed to have been delivered upon confirmation of receipt by telephone. Notices of change of address shall be effective upon receipt.

#### 24.8 **Governing Law**

This Agreement shall be governed by and construed in accordance with the laws of the State of New York without giving effect to any choice or conflict or law provision or rule.

#### 24.9 **Arbitration**

(a) Any dispute under this Agreement or the other Transaction Documents which is not settled by mutual consent (whether pursuant to the provisions in Clause 19 hereof or otherwise) shall be finally settled by binding arbitration, conducted in accordance with the Commercial Arbitration Rules of the American Arbitration Association by one (1) arbitrator appointed in accordance with said rules. Such arbitrator shall be reasonably satisfactory to each of the Parties; provided, that if the Parties are unable to agree upon the identity of such arbitrator within 15 days of demand by either Party, then either Party shall have the right to petition the Presiding Justice to appoint an arbitrator.

The arbitration shall be held in New York, New York and the arbitrator shall be an independent expert in pharmaceutical product development and marketing (including clinical development and regulatory affairs).

(b) The arbitrator shall determine what discovery will be permitted, consistent with the goal of limiting the cost and time which the Parties must expend for discovery; provided the arbitrator shall permit such discovery as they deem necessary to permit an equitable resolution of the dispute.

Any written evidence originally in a language other than English shall be submitted in English translation accompanied by the original or a true copy thereof.

The costs of the arbitration, including administrative and arbitrators' fees, shall be shared equally by the Parties and each Party shall bear its own costs and attorneys' and witness' fees incurred in connection with the arbitration.

(c) In rendering judgment, the arbitrator shall be instructed by the Parties that he shall be permitted to select solely from between the proposals for resolution of the relevant issue presented by each Party, and not any other proposal.

A disputed performance or suspended performances pending the resolution of the arbitration must be completed within thirty (30) days following the final decision of the arbitrators or such other reasonable period as the arbitrators determine in a written opinion.

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(d) Any arbitration under the Transaction Documents shall be completed within one year from the filing of notice of a request for such arbitration.

The arbitration proceedings and the decision shall not be made public without the joint consent of the Parties and each Party shall maintain the confidentiality of such proceedings and decision unless otherwise permitted by the other Party.

(e) The Parties agree that the decision shall be the sole, exclusive and binding remedy between them regarding any and all disputes, controversies, claims and counterclaims presented to the arbitrators. Application may be made to any court having jurisdiction over the Party (or its assets) against whom the decision is rendered for a judicial recognition of the decision and an order of enforcement.

**24.10 Severability:**

If any provision in this Agreement is agreed by the Parties to be, deemed to be or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto, such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable or, if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of such agreement or such earlier date as the Parties may agree, and the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

**24.11 Amendments:**

No amendment, modification or addition hereto shall be effective or binding on any Party unless set forth in writing and executed by a duly authorized representative of all Parties.

**24.12 Waiver:**

No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any future breach or failure to perform or of any other right arising under this Agreement.

**24.13 Assignment:**

None of the Parties shall be permitted to assign its rights or obligations hereunder without the prior written consent of the other Parties except as follows:

24.13.1 Elan, EIS and/or Isis shall have the right to assign their rights and obligations hereunder to their Affiliates provided, however, that such assignment does not result in adverse tax consequences for any other Parties.

24.13.2 Elan and EIS shall have the right to assign their rights and obligations hereunder to an off-balance sheet special purpose entity established by Elan or EIS.

24.13.3 Elan, EIS and/or Isis shall have the right to assign or otherwise transfer their rights and obligations hereunder in connection with a sale of all or substantially all of the business of such Party to which the transaction Documents relate, whether by merger, sale of stock, sale of assets or otherwise; provided however, that Elan or EIS may not assign or otherwise transfer (including by merger, sale of stock or sale of assets) its rights to fund Orasense or extend the Research Term.

**24.14 Whole Agreement/No Effect on Other Agreements:**

This Agreement (including the Schedules attached hereto) and the other Transaction Documents set forth all of the agreements and understandings between the Parties with respect to the subject

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matter hereof, and supersedes and terminates all prior agreements and understandings between the Parties with respect to the subject matter hereof. There are no agreements or understandings with respect to the subject matter hereof, either oral or written, between the Parties other than as set forth in this Agreement and the other Transaction Documents.

In the event of any ambiguity or conflict arising between the terms of this Agreement and those of the Orasense Memorandum of Association and Bye-Laws, the terms of this Agreement shall prevail.

No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between any of the Parties unless specifically referred to, and solely to the extent provided herein. In the event of a conflict between the provisions of this Agreement and the provisions of the License Agreements, the terms of the License Agreements shall prevail.

**24.16 Successors:** This Agreement shall be binding upon and inure to the benefit of the Parties hereto, their successors and permitted assigns.

[Signature Page Follows]

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IN WITNESS WHEREOF, the Parties hereto have executed this Agreement on the day first set forth above.

SIGNED

BY: /s/ KEVIN INSLEY

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for and on behalf of  
ELAN CORPORATION, PLC

in the presence of: /s/ DEBBIE BURYJ  
\_\_\_\_\_

SIGNED

BY: /s/ DEBBIE BURYJ  
\_\_\_\_\_

for and on behalf of  
ELAN INTERNATIONAL SERVICES, LTD.

in the presence of: /s/ KEVIN INSLEY  
\_\_\_\_\_

SIGNED

BY: /s/ B. LYNNE PARSHALL  
\_\_\_\_\_

for and on behalf of  
ISIS PHARMACEUTICALS, INC.

in the presence of: /s/ GRANTLAND E. BRYCE  
\_\_\_\_\_

SIGNED

BY: /s/ E.C.J  
\_\_\_\_\_

for and on behalf of  
ORASENSE LTD.

in the presence of: /s/ ILLEGIBLE  
\_\_\_\_\_

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**SCHEDULE 1**

**ORASENSE COLLABORATION INTELLECTUAL PROPERTY**

[\*\*\*]

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**SCHEDULE 2**

**RESEARCH PLAN(1)**

[\*\*\*]

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- (1) Promptly following the Effective Date, the Management Committee shall clarify the Research Plan as necessary to further detail the objectives of Orasense through the end of the Research Term.

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**Table 1. 2002 Oral Clinical Studies**

[\*\*\*]

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**BUDGET**

[\*\*\*]

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**ORASENSE BUDGET ASSUMPTIONS**

[\*\*\*]

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## QuickLinks

[AMENDED AND RESTATED SUBSCRIPTION, JOINT DEVELOPMENT AND OPERATING AGREEMENT ELAN CORPORATION, PLC ELAN INTERNATIONAL SERVICES, LTD. ISIS PHARMACEUTICALS, INC. AND ORASENSE LTD. October 24, 2002](#)

Execution Copy

**TERMINATION AGREEMENT**  
**ELAN CORPORATION, PLC**  
**ELAN PHARMA INTERNATIONAL LIMITED**  
**ELAN INTERNATIONAL SERVICES, LTD.**  
**ISIS PHARMACEUTICALS, INC.**

**AND**  
**HEPASENSE LTD**

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**THIS TERMINATION AGREEMENT** made as of this 5<sup>th</sup> day of November, 2002 (this "**Agreement**")

**AMONG:-**

- (1) **ELAN CORPORATION, PLC**, a public limited company incorporated under the laws of Ireland and having its registered office at Lincoln House, Lincoln Place, Dublin 2, Ireland ("**Elan Corp**");
- (2) **ELAN PHARMA INTERNATIONAL LIMITED**, a private limited company incorporated under the laws of Ireland, and having its registered office at WIL House, Shannon Business Park, Shannon, County Clare, Ireland ("**EPIL Shannon**");
- (3) **ELAN INTERNATIONAL SERVICES, LTD.**, an exempted limited liability company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("**EIS**");
- (4) **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation having its principal place of business at 2292 Faraday Avenue, Carlsbad, CA 92008, United States of America ("**Isis**"); and
- (5) **HEPASENSE, LTD.**, an exempted company incorporated under the laws of Bermuda, and having its registered office at Clarendon House, 2 Church St., Hamilton, Bermuda ("**Hepasense**").

**RECITALS:**

- A. The Parties entered into various agreements whereby Elan Corp, EPIL Shannon, EIS and Isis established the joint venture company, Hepasense, and Elan Corp, EPIL Shannon and Isis each licensed certain intellectual property to Hepasense for a specified field of use. Specifically:
  - (i) Elan Corp, EIS, EPIL Shannon, Isis and Hepasense entered into a Subscription, Joint Development and Operating Agreement dated 14 January 2000 (the "**JDOA**");



(ii) Elan Corp, EPIL Shannon, Isis and Hepasense entered into a License Agreement dated 14 January 2000 (the "**Elan License Agreement**");

(iii) Isis, Hepasense, Elan Corp and EPIL Shannon entered into a License Agreement dated 14 January 2000 (the "**Isis License Agreement**");

(iv) Isis, Elan Corp, EIS and EPIL Shannon entered into a Funding Agreement dated 14 January 2000 (the "**Funding Agreement**").

B. The JDOA and Funding Agreement are together defined in this Agreement as the "**Hepasense Agreements**".

C. The Parties also entered into a certain Securities Purchase Agreement dated 14 January 2000, as amended by that certain Amendment No. 1 to Securities Purchase Agreement dated 25 April 2002 (the "**Securities Purchase Agreement**"), whereby Isis sold and EIS and EPIL Shannon purchased certain securities of Isis and such parties agreed to certain matters related to the ownership of such securities.

D. The Parties now wish to (i) terminate in full the Hepasense Agreements as set forth below, (ii) set forth their agreement in relation to other matters and (iii) amend certain agreements as set forth below in relation to matters related to security holdings in Isis.

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**IN CONSIDERATION OF THE MUTUAL COVENANTS CONTAINED HEREIN, AND OTHER GOOD AND VALUABLE CONSIDERATION, THE RECEIPT AND ADEQUACY OF WHICH ARE HEREBY ACKNOWLEDGED, IT IS HEREBY AGREED AS FOLLOWS:**

**1 DEFINITIONS:**

**Capitalised terms used in this Agreement shall have the same meanings assigned to them in the Hepasense Agreements or the License Agreements (as applicable), unless such terms are expressly defined to the contrary in this Agreement.**

"**Affiliate**" shall mean any corporation or entity controlling, controlled or under the common control of any other corporation or entity, excluding, in the case of Elan Corp, an Elan JV. For the purpose of this definition, (i) "control" shall mean direct or indirect ownership of fifty percent (50%) or more of the stock or shares entitled to vote for the election of directors; and (ii) notwithstanding the above, neither Hepasense nor EPIL II, shall be an Affiliate of Elan Corp, EIS or Isis.

"**Balance Sheet**" shall mean the unaudited balance sheet of Hepasense made up to the Balance Sheet Date, as set forth in Schedule 3.2.

"**Balance Sheet Date**" shall mean 30 June 2002.

"**Effective Date**" shall mean the date of this Agreement.

"**Elan**" shall mean Elan Corp and its Affiliates.

"**Elan Improvements**" shall have the meaning set forth in the JDOA.

"**Elan JV**" shall mean an entity that Elan and a third party (i) establish or have established; (ii) take shareholdings in or have a right to take shareholdings in; and (iii) grant certain licenses in and to certain intellectual property rights for the purpose of implementing a strategic alliance.

"**Elan Know-How**" shall have the meaning set forth in the Elan Licence Agreement.

"**Elan Patents**" shall have the meaning set forth in the Elan Licence Agreement.

"**EPIL II**" shall mean Elan Pharmaceuticals Investment II, Ltd. an exempted limited liability company incorporated under the laws of Bermuda.

"**Exchange Right**" has the meaning assigned to such term in the Certificate of Designations of Series B Preferred Shares of Isis issued on 14 January 2000.

"**Force Majeure**" shall mean causes beyond a Party's reasonable control, including, without limitation, acts of God, fires, strikes, acts of war, or intervention of a governmental authority.

"**Hepasense**" shall mean Hepasense Ltd. and its Affiliates.

"**Hepasense Trademark**" shall mean Hepasense, Ltd..

"**Hepasense Intellectual Property**" shall mean Hepasense Intellectual Property as such term is defined in the JDOA.

"**Isis**" shall mean Isis Pharmaceuticals, Inc. and its Affiliates.

"**Isis Improvements**" shall mean improvements to the Isis Patents and/or the Isis Know-How, developed (i) by Isis outside the Project, (ii) by Isis, Elan or Hepasense or by a third party (under contract with Hepasense, Elan or Isis) pursuant to the Project, and/or (iii) jointly by any combination of Isis, Elan, Hepasense or a third party (under contract with Hepasense, Elan or Isis) pursuant to the Project.

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"**Isis Know-How**" shall mean Isis Know-How (as such term is defined in the Isis Licence Agreement).

"**Isis Patents**" shall mean Isis Patents (as such term is defined in the Isis Licence Agreement).

"**License Agreements**" shall mean the Elan License Agreement and the Isis License Agreement, collectively.

"**Party**" shall mean Elan Corp, EIS, EPIL Shannon, Isis or Hepasense, as the case may be, and "**Parties**" shall mean all such parties together.

"**Project**" shall have the meaning set forth in the JDOA.

"**Territory**" shall mean all the countries of the world.

"**United States Dollar**" and "**US\$**" and "**\$**" shall mean the lawful currency of the United States of America.

## 2 **TERMINATION OF THE HEPASENSE AGREEMENTS**

2.1 Subject to the provisions of Clause 2.3 hereof, the Parties hereby agree to terminate the Hepasense Agreements, including without limitation, those provisions expressly stated to survive termination, in each case with effect from the Effective Date.

Subject to Clause 2.2, all the provisions of the Hepasense Agreements shall terminate forthwith with effect from the Effective Date and be of no further legal force or effect.

2.2 For the avoidance of doubt, the Parties agree that Clause 17.1 of the JDOA, Clause 17.2 of the JDOA and Clause 17.3 of the JDOA shall be terminated forthwith with effect from the Effective Date and be of no further legal force or effect.

The Parties acknowledge that the provisions of Clause 17.4 of the JDOA (the "**Tag-along Provisions**") shall continue in full force and effect as between EPIL II and Isis as holders of certain shares in Hepasense. Solely for the purposes of the Tag-along Provisions, any definitions or additional clauses of the JDOA required to give effect to the Tag-along Provisions will be deemed to survive termination.

The Parties agree that EPIL II is a third party beneficiary of this Clause 2.2.

2.3 For the avoidance of doubt and without prejudice to the generality of the foregoing Clause 2.1, the Parties hereby acknowledge and agree as follows as of the Effective Date:

2.3.1 the nominees on the Management Committee of EIS shall be deemed to have been removed from the Management Committee by EIS;

2.3.2 the nominees on the R&D Committee of Elan (as such term is used in the JDOA), shall be deemed to have been removed from the R&D Committee by Elan (as such term is used in the JDOA);

2.3.3 Elan shall terminate or shall cause to be terminated any and all research and development work being conducted in connection with or pursuant to any Research and Development Program of Hepasense, the Hepasense Agreements, or otherwise on behalf of Hepasense;

2.3.4 the Parties shall terminate or cause to be terminated any and all technical services and assistance being conducted in connection with the Hepasense Agreements;

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2.3.5 for the avoidance of doubt, none of the Parties shall have any obligation to provide working capital, research or development funding, or other funding or financing of any nature to Hepasense;

2.3.6 for the further avoidance of doubt, the Parties agree that Elan has had no obligation to provide working capital, research or development funding, or other funding or financing of any nature to Hepasense following 30 June 2002;

2.3.7 Elan shall not have any obligation to pay any milestone payment or make any milestone investment to or in Hepasense or Isis whether relating to the Project, the achievement of any objectives set forth therein or otherwise.

2.4 Each of the Parties acknowledges and agrees with the other Parties that, as of the Effective Date, no monies are owed or are refundable by any of the Parties to the others pursuant to the Hepasense Agreements or the License Agreements, other than such sums owed to Isis and/or Elan by Hepasense pursuant to the JDOA as are set forth on Schedule 2.4, to be paid promptly after the Effective Date.

## 3 **REPRESENTATIONS, WARRANTIES, CONFIRMATIONS AND INDEMNITIES**

### 3.1 **Sub-licenses:**

Isis and Hepasense jointly and severally represents and warrants to the other Parties that it has not granted any sub-licences or any other rights of any nature to any third parties pursuant to the Elan License Agreement or the Isis License Agreement.

### 3.2 **Balance Sheet:**

Isis represents and warrants to the other Parties that the Balance Sheet is accurate and that, since the Balance Sheet Date, there has been no material adverse change in the financial position or prospects of Hepasense.

Isis represents and warrants to the other Parties that there are no other creditors of Hepasense other than as described in the Balance Sheet.

### 3.3 **Third party agreements / Orders / Claims:**

3.3.1 Each of the Parties confirms to the other Parties hereto that, as of the Effective Date, to its actual knowledge, Hepasense is not a party to, or bound by, any judgement, order, decree or other directive of or stipulation with any court or any governmental or regulatory authority.

3.3.2 Isis and Hepasense jointly and severally represents and warrants to the other Parties that Hepasense is not a party to, or bound by, or is a third party beneficiary of any agreement with any third party, except for the Hepasense Agreements and the License Agreements, other than as set out in Schedule 3.3.2 ("**Hepasense Third Party Agreement(s)**").

For the avoidance of doubt and with reference to the indemnity Clause 3.6.1, the Parties agree that the indemnity in Clause 3.6.1 shall extend to any claims, losses, liabilities or damages arising from such Hepasense Third Party Agreements.

3.3.3 Where Elan is a party to any Hepasense Third Party Agreement, the Parties agree as follows:-

(1) Elan will, as of the Effective Date, terminate its relationship thereunder with any other Party hereto which may be a party thereto, and cease to have any obligations of any nature whatsoever to any such Party thereunder;

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(2) immediately following the Effective Date:

(i) Isis and/or Hepasense will notify the relevant third party to the Hepasense Third Party Agreement(s) in writing that Elan has terminated the Hepasense Agreements and will use best efforts to procure that the relevant third party executes a full release agreement ("**Hepasense Third Party Release**") in favour of Elan releasing Elan from all obligations of any nature whatsoever to the relevant third party under the relevant Hepasense Third Party Agreement; and

(ii) immediately following the execution of any Hepasense Third Party Release, Elan shall assign any rights it has under the relevant Hepasense Third Party Agreement to Hepasense.

(3) if Isis and/or Hepasense have not provided Elan with the Hepasense Third Party Release within 30 days of the Effective Date, the obligations of Isis and Hepasense under this Cause 3.3.3 shall continue but Elan will also be free to contact the relevant third party directly to effect the execution by the relevant third party of such a Hepasense Third Party Release.

3.3. Each of the Parties confirms to the other Parties hereto that, as of the Effective Date, to its actual knowledge, there are no claims, suits or proceedings pending or threatened against Hepasense.

#### 3.4 **Regulatory Applications:**

Each of the Parties confirms to the other Parties that, prior to and as of the Effective Date, no regulatory applications have been filed by Hepasense or by any Party with any government authority in any part of the world for any Product, Hepasense Intellectual Property, or otherwise howsoever in relation to the Project other than such regulatory applications as are set out in Schedule 3.4.

#### 3.5 **Exclusion of warranties / liability:**

**EXCEPT AS EXPRESSLY PROVIDED IN THIS AGREEMENT, ALL OTHER WARRANTIES, CONDITIONS OR REPRESENTATIONS, EXPRESS OR IMPLIED, STATUTORY OR OTHERWISE, ARE HEREBY EXPRESSLY EXCLUDED BY THE PARTIES.**

**NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, NO PARTY SHALL BE LIABLE TO ANY OTHER PARTY BY REASON OF ANY REPRESENTATION OR WARRANTY, CONDITION OR OTHER TERM OR ANY DUTY OF COMMON LAW, OR UNDER THE EXPRESS TERMS OF THIS AGREEMENT, FOR ANY CONSEQUENTIAL SPECIAL OR INCIDENTAL OR PUNITIVE LOSS OR DAMAGE (WHETHER FOR LOSS OF CURRENT OR FUTURE PROFITS, LOSS OF ENTERPRISE VALUE OR OTHERWISE) AND WHETHER OCCASIONED BY THE NEGLIGENCE OF THE RESPECTIVE PARTIES, THEIR EMPLOYEES OR AGENTS OR OTHERWISE.**

#### 3.6 **Indemnity by Isis on future activities of Hepasense:**

3.6.1 Isis and Hepasense jointly and severally hereby agrees to indemnify and hold harmless Elan Corp, EIS and their respective Affiliates, officers, directors and employees, and any person holding office on or prior to the Effective Date as an EIS Director (as defined in the JDOA) (or any alternate director of the EIS Director) or as a member of the Management Committee or the R&D Committee (each such person or entity referred to as an "**Indemnified Party**") against any claims, losses, liabilities or damages and expenses (including reasonable attorneys' fees and expenses) incurred or sustained by such Indemnified Party to the extent based upon or arising out of any claim or proceedings made against Hepasense or an Indemnified Party which relate in any way to the activities of Hepasense, past present or future, including without limitation, claims arising with respect to the conduct of clinical trials (if any) by Hepasense, or by Isis or any other person or entity on behalf of Hepasense whether in connection with the Project or otherwise ("**Claims**"), [\*\*\*]

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3.6.2 [\*\*\*].

3.6.3 For the avoidance of doubt and without prejudice to the generality of, or the limitations contained in, Clause 3.6.1, Isis and Hepasense jointly and severally shall indemnify and hold harmless Elan against any claims, losses, liabilities or damages and expenses (including reasonable attorneys' fees and expenses) which may arise in relation to any claim or proceedings made against Elan Corp or any of its Affiliates alleging infringement or other unauthorised use of the proprietary rights of a third party arising from the manufacture, importation, use, offer for sale, sale or other commercialization of the Product and the Hepasense Intellectual Property or any technology related thereto.

3.6.4 For the avoidance of doubt and with reference to the indemnity in Clause 3.6.1 the Parties acknowledge that a clinical trial was carried out by Isis on behalf of Hepasense with respect to the development of the Product and the Parties agree that the indemnity in Clause 3.6.1 shall extend to any

claims, losses, liabilities or damages arising from such clinical trial(s).

3.6.5 An Indemnified Party will (i) notify Isis in writing of any Claims with respect to which the Indemnified Party intends to claim indemnification as soon as practicable after the Indemnified Party becomes aware of any such Claims; (ii) permit Isis to assume the defense thereof with counsel selected by Isis; and (iii) cooperate with Isis, at Isis' expense, in the defense thereof.

If Isis does not elect to assume the defense of any Infringement Claim, then, upon 10 days written notice to Isis, the Indemnified Party may assume the defense of the Indemnification Claim. In such event, the Indemnified Party shall be entitled as part of its damages to indemnification for the reasonable costs of such defense.

3.6.6 An Indemnified Party will have the right to participate and be represented (at Isis' expense) by legal counsel of the Indemnified Party's choice in all proceedings and negotiations, if representation by counsel retained by Isis would be inappropriate due to actual or potential differing interests between the Indemnified Party and any other party represented by such counsel in such proceedings.

3.6.7 An Indemnified Party will not settle or compromise any Claim without the prior written consent of Isis, which consent may not be unreasonably withheld. Isis will not settle or compromise any Claim in any manner that admits fault on the part of the Indemnified Party without the express prior written consent of the Indemnified Party, which consent may be withheld for any reason or no reason.

3.6.8 Failure of the Indemnified Party to deliver notice to Isis within a reasonable time after becoming aware of potential Claims will not relieve Isis of any liability to the Indemnified Party pursuant to this Clause, except to the extent such delay prejudices Isis' ability to defend the Claim.

3.6.9 Prior to the Effective Date, Isis shall furnish Elan Corp with copies of all policies of comprehensive general liability insurance and/or other insurance coverages (the "**Policies**") which it holds in respect of the clinical trial(s) referred to in Clause 3.6.4.

Isis shall be obliged to maintain the Policies for a period of [\*\*\*] from the Effective Date maintaining at all times at a minimum, the levels of cover evidenced in the Policies, and shall, at the reasonable request of Elan Corp from time to time, furnish to Elan Corp evidence that all premiums or other payments on the Policies are fully paid up and the Policies are subsisting.

[\*\*\*]

### 3.7 **Organization and authority:**

Each of the Parties represents and warrants to the other Parties that it is a corporation duly organised and validly existing under the laws of its jurisdiction of organisation and has all the requisite corporate power and authority to enter into this Agreement and to carry out the transactions contemplated hereby.

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### 3.8 **Approvals:**

Each of the Parties represents and warrants to the other Parties that no permit, authorization, consent or approval of or by ("**Approval**"), or any notification of or filing with ("**Filing**"), any person or entity (governmental or otherwise) is required in connection with the execution, delivery or performance of this Agreement by such Party, or if any such Approval or Filing is so required, that same has been obtained or filed prior to the Effective Date.

### 3.9 **Trademark Applications**

Isis and Hepasense jointly and severally represents and warrants to the other Parties that it has not filed for any trademark protection or has not adopted any new trademark, apart from the Hepasense Trademark, in connection with its business or any product or service provided thereunder.

## 4 **INTELLECTUAL PROPERTY**

### 4.1 **Ownership:**

On and following the Effective Date:

4.1.1 For the avoidance of doubt, the Elan Patents and/or the Elan Know-How shall remain the sole and exclusive property of Elan.

Elan confirms that no Elan Improvements were developed pursuant to the Project, or otherwise pursuant to the Hepasense Agreements or the License Agreements.

4.1.2 For the avoidance of doubt, the Isis Patents and the Isis Know-How and/or the Isis Improvements ([\*\*\*] as set out in Schedule 4.1.2) shall remain the sole and exclusive property of Isis.

4.1.3 All Hepasense Intellectual Property ([\*\*\*] as set out in Schedule 4.1.3) shall remain the sole and exclusive property of Hepasense.

## 5 **RIGHTS RELATED TO SECURITIES**

5.1 Nothing contained herein shall constitute a waiver of any right of EPIL Shannon, EIS or EPIL II or any of their respective successors and assigns with respect to their respective ownership of securities in Isis under any agreements of any kind in existence with Isis with respect thereto or under the charter or other governance documents of Isis, which agreements shall remain unmodified and in full force and effect, except as set forth in this Clause 5 and in Schedule 5.1.

## 6 **COMPLETION**

6.1 On the Effective Date, Elan and Isis shall take or (to the extent that the same is within its powers) cause to be taken the following steps prior to or at directors and shareholders meetings of Hepasense, or such other meetings, as appropriate:

6.1.1 the change of the registered office of Hepasense from at Clarendon House, 2 Church St., Hamilton, Bermuda;

6.1.2 the modification, as appropriate, by board resolutions of Hepasense of matters such as the removal of EIS as book keeper for Hepasense, the removal of EIS representatives as authorised signatories of Hepasense's bank account, the resignation of the Company Secretary and any other related matters whatsoever; and

6.1.3 any other steps required by this Agreement.

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## 7 CONFIDENTIALITY

### 7.1 Confidentiality:

7.1.1 The Parties agree that it may be necessary pursuant to this Agreement, from time to time, to disclose to each other confidential and proprietary information, including without limitation, inventions, trade secrets, specifications, designs, data, know-how and other proprietary information, processes, services and business of the disclosing Party.

The foregoing shall be referred to collectively as "**Additional Confidential Information**".

The Parties also agree that it may have been necessary to disclose to each other Confidential Information (as defined in the JDOA) pursuant to the Hepasense Agreements or the License Agreements.

Together Additional Confidential Information and Confidential Information shall be referred to collectively as "**Proprietary Information**".

7.1.2 Save as otherwise specifically provided herein, and subject to Clause 7.2 and 7.3, each Party shall disclose Proprietary Information of the other Party only to those employees, representatives and agents requiring knowledge thereof in connection with fulfilling the Party's obligations under this Agreement, and not to any other third party.

Each Party further agrees to inform all such employees, representatives and agents of the terms and provisions of this Agreement relating to Proprietary Information and their duties hereunder and to obtain their agreement hereto as a condition of receiving Proprietary Information.

Each Party shall exercise the same standard of care as it would itself exercise in relation to its own confidential information (but in no event less than a reasonable standard of care) to protect and preserve the proprietary and confidential nature of the Proprietary Information disclosed to it by the other party.

Each Party shall promptly, upon request of the other Party, return all documents and any copies thereof containing Proprietary Information belonging to, or disclosed by, such other Party, save that it may retain one copy of the same solely for the purposes of ensuring compliance with this Clause 7.

7.1.3 Any breach of this Clause 7 by any person informed by one of the Parties is considered a breach by the Party itself.

7.1.4 Proprietary Information shall be deemed not to include:

- (1) information which is in the public domain;
- (2) information which is made public through no breach of this Agreement;
- (3) information which is independently developed by a Party, as evidenced by such Party's records;
- (4) information that becomes available to a receiving Party on a non-confidential basis, whether directly or indirectly, from a source other than the other Party, which source did not acquire this information on a confidential basis.

7.1.5 The provisions relating to confidentiality in this Clause 7 shall remain in effect during the term of this Agreement, and for a period of 10 years following the Effective Date of this Agreement.

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7.1.6 The Parties agree that the obligations of this Clause 7 are necessary and reasonable in order to protect the Parties' respective businesses, and each Party agrees that monetary damages may be inadequate to compensate a Party for any breach by the other Party of its covenants and agreements set forth herein.

The Parties agree that any such violation or threatened violation may cause irreparable injury to a Party and that, in addition to any other remedies that may be available, in law and equity or otherwise, each Party shall be entitled to seek injunctive relief against the threatened breach of the provisions of this Clause 7, or a continuation of any such breach by the other Party, specific performance and other equitable relief to redress such breach together with damages and reasonable counsel fees and expenses to enforce its rights hereunder.

### 7.2 Announcements:

7.2.1 Subject to Clause 7.3, no announcement or public statement concerning the existence, subject matter or any term of this Agreement shall be made by or on behalf of any Party without the prior written approval of the other Party or Parties.

The terms of any such announcement shall be agreed in good faith by the Parties.

### 7.3 **Required Disclosures:**

7.3.1 A Party (the "**Disclosing Party**") will be entitled to make an announcement or public statement concerning the existence, subject matter or any term of this Agreement, or to disclose Proprietary Information that the Disclosing Party is required to make or disclose pursuant to:

- (1) a valid order of a court or governmental authority; or
- (2) any other requirement of law or any securities or stock exchange;

provided that if the Disclosing Party becomes legally required to make such announcement, public statement or disclosure hereunder, the Disclosing Party shall give the other Party or Parties prompt notice of such fact to enable the other Party or Parties to seek a protective order or other appropriate remedy concerning any such announcement, public statement or disclosure.

The Disclosing Party shall fully co-operate with the other Party or Parties in connection with that other Party's or Parties' reasonable efforts to obtain any such order or other remedy.

If any such order or other remedy does not fully preclude announcement, public statement or disclosure, the Disclosing Party shall make such announcement, public statement or disclosure only to the extent that the same is legally required.

7.3.2 Each of the Parties shall be entitled to provide a copy of this Agreement (and any subsequent amendments hereto) and the License Agreements to a potential third party purchaser in connection with Clause 9.2 **provided that** the relevant third party purchaser or assignee has entered into a confidentiality agreement on terms no less protective than the terms of this Clause 7.

## 8 **WAIVER OF ACCRUED RIGHTS/MUTUAL RELEASES**

8.1 With effect from the Effective Date, each Party and each of its Affiliates ("**Releasor**"):-

8.1.1 waives any accrued rights that Releasor may have accrued against the other Parties and each of its Affiliates, officers, directors, representative, agents and employees and the assigns and successors in interest of any of the foregoing entities ("**Releasees**"), whether known or unknown, foreseen or unforeseen, fixed or contingent, of any nature whatsoever from the beginning of time to the Effective Date under the Hepasense Agreements or the License Agreements; and

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8.1.2 fully and finally releases and discharges the Releasees from any and all manner of actions, claims, promises, debts, sums of money, demands, obligations, in law or in equity, directly or indirectly, whether known or unknown, foreseen or unforeseen, fixed or contingent, of any nature whatsoever that Releasor may have by reason of any act, omission, matter, provision, cause or thing whatsoever from the beginning of time to the Effective Date under the Hepasense Agreements or the License Agreements.

8.2 For the avoidance of doubt the provisions of this Clause 8 shall not in any way act as a waiver by any of the Parties in respect of any of the provisions set forth in this Agreement (including, for the avoidance of doubt, Clause 3.6.1).

## 9 **GENERAL**

9.1 **Governing law and jurisdiction:**

9.1.1 This Agreement shall be governed by and construed in accordance with the laws of the State of New York without regard to conflicts of law principles under the laws of the State of New York.

9.1.2 Any dispute under this Agreement which is not settled by mutual consent shall be finally settled by binding arbitration, conducted in accordance with the Commercial Arbitration Rules of the American Arbitration Association by one (1) arbitrator appointed in accordance with said rules. Such arbitrator shall be reasonably satisfactory to each of the Parties; provided, that if the Parties are unable to agree upon the identity of such arbitrator within 15 days of demand by either Party, then either Party shall have the right to petition the Presiding Justice to appoint an arbitrator.

9.1.3 The arbitration shall be held in New York, New York and the arbitrator shall be an independent expert in pharmaceutical product development and marketing (including clinical development and regulatory affairs).

9.1.4 The arbitrator shall determine what discovery will be permitted, consistent with the goal of limiting the cost and time which the Parties must expend for discovery; provided the arbitrator shall permit such discovery as they deem necessary to permit an equitable resolution of the dispute.

9.1.5 Any written evidence originally in a language other than English shall be submitted in English translation accompanied by the original or a true copy thereof.

9.1.6 The costs of the arbitration, including administrative and arbitrators' fees, shall be shared equally by the Parties and each Party shall bear its own costs and attorneys' and witness' fees incurred in connection with the arbitration.

9.1.7 In rendering judgement, the arbitrator shall be instructed by the Parties that he shall be permitted to select solely from between the proposals for resolution of the relevant issue presented by each Party, and not any other proposal.

9.1.8 A disputed performance or suspended performances pending the resolution of the arbitration must be completed within thirty (30) days following the final decision of the arbitrators or such other reasonable period as the arbitrators determine in a written opinion.

9.1.9 Any arbitration under the this Agreement shall be completed within one year from the filing of notice of a request for such arbitration.

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9.1.10 The arbitration proceedings and the decision shall not be made public without the joint consent of the Parties and each Party shall maintain the confidentiality of such proceedings and decision unless otherwise permitted by the other Party.

9.1.11 The Parties agree that the decision shall be the sole, exclusive and binding remedy between them regarding any and all disputes, controversies, claims and counterclaims presented to the arbitrators. Application may be made to any court having jurisdiction over the Party (or its assets) against whom the decision is rendered for a judicial recognition of the decision and an order of enforcement.

## 9.2 *Assignment*

This Agreement shall not be assigned by any Party without the prior written consent of the others, save that any Party:

9.2.1 may assign this Agreement in whole or in part and delegate its duties hereunder to its Affiliate or Affiliates without such consent; and

9.2.2 may assign its rights and obligations to a successor (whether by merger, stock sale, consolidation, reorganisation or other similar event) or purchaser of all or substantially all of its assets relating to such Party's technology related to this Agreement, provided that such successor or purchaser has agreed in writing to assume all of such Party's rights and obligations hereunder and a copy of such assumption is provided to the other Parties.

For the avoidance of doubt, nothing in this Clause 9.2 shall affect the provisions governing assignment of securities in Schedule 5.1 hereof.

## 9.3 *Notices*

9.3.1 Any notice to be given under this Agreement shall be sent in writing in English by registered airmail, internationally recognized courier or telefaxed to the following addresses:

If to Hepasense at:

Hepasense Limited  
Clarendon House  
2 Church St.  
Hamilton  
Bermuda  
Attention: B. Lynne Parshall, Esq.  
Telephone: 760-603-2460  
Fax: 760-931-9639

with a copy to Isis at:

2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: B. Lynne Parshall, Esq.  
Telephone: 760-603-2460  
Fax: 760-931-9639

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If to Isis at:

Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, CA 92008  
Attention: B. Lynne Parshall, Esq.  
Telephone: 760-603-2460  
Fax: 760-931-9639

If to Elan, EIS and/or EPIL Shannon at:

Elan Corporation, plc  
Elan Pharma International Limited  
Elan International Services, Ltd.  
C/o Elan International Services, Ltd.  
102 St. James Court  
Flatts,  
Smiths FL04  
Bermuda  
Attention: Secretary  
Telephone: 441 292 9169  
Fax: 441 292 2224

or to such other address(es) and telefax numbers as may from time to time be notified by any Party to the others hereunder.

9.3.2 Any notice sent by mail shall be deemed to have been delivered within seven (7) working days after dispatch or delivery to the relevant courier and notice sent by fax shall be deemed to have been delivered upon confirmation receipt. Notice of change of address shall be effective upon receipt.

#### 9.4 **Waiver**

No waiver of any right under this Agreement shall be deemed effective unless contained in a written document signed by the Party charged with such waiver, and no waiver of any breach or failure to perform shall be deemed to be a waiver of any future breach or failure to perform or of any other right arising under this Agreement.

#### 9.5 **Severability**

If any provision in this Agreement is agreed by the Parties to be, or is deemed to be, or becomes invalid, illegal, void or unenforceable under any law that is applicable hereto:

9.5.1 such provision will be deemed amended to conform to applicable laws so as to be valid and enforceable; or

9.5.2 if it cannot be so amended without materially altering the intention of the Parties, it will be deleted, with effect from the date of this Agreement or such earlier date as the Parties may agree, and the validity, legality and enforceability of the remaining provisions of this Agreement shall not be impaired or affected in any way.

#### 9.6 **Further Assurances**

At the request of any of the Parties, the other Party or Parties shall (and shall use reasonable efforts to procure that any other necessary parties shall) execute and perform all such documents, acts and things as may reasonably be required subsequent to the signing of this Agreement for assuring to or vesting in the requesting Party the full benefit of the terms hereof.

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#### 9.7 **Successors**

This Agreement shall be binding upon and inure to the benefit of the Parties hereto and their respective successors and permitted assigns.

#### 9.8 **Amendments**

No amendment, modification or addition hereto shall be effective or binding on any Party unless set forth in writing and executed by a duly authorized representative of each Party.

#### 9.9 **Counterparts**

This Agreement may be executed in any number of counterparts, each of which when so executed shall be deemed to be an original and all of which when taken together shall constitute this Agreement.

#### 9.10 **Costs**

Each Party shall bear its own costs and expenses in connection with the transactions contemplated by this Agreement.

#### 9.11 **Force Majeure:**

Neither Party to this Agreement shall be liable for failure or delay in the performance of any of its obligations hereunder if such failure or delay results from Force Majeure, but any such failure or delay shall be remedied by such Party as soon as practicable.

#### 9.12 **Relationship of the Parties:**

The Parties are independent contractors under this Agreement. Nothing herein contained shall be deemed to create or establish an employment, agency, joint venture, or partnership relationship between the Parties or any of their agents or employees, or any other legal arrangement that would impose liability upon one Party for the act or failure to act of the other Party. Neither Party shall have any express or implied power to enter into any contracts, commitments or negotiations or to incur any liabilities in the name of, or on behalf of, the other Party, or to bind the other Party in any respect whatsoever.

#### 9.13 **Entire agreement:**

9.13.1 this Agreement and the License Agreements set forth all of the agreements and understandings between the Parties with respect to the subject matter hereof. There are no agreements or understandings with respect to the subject matter hereof, either oral or written, between the Parties other than as set forth in this Agreement.

9.13.2 No provision of this Agreement shall be construed so as to negate, modify or affect in any way the provisions of any other agreement between the Parties unless specifically provided herein and only to the extent so specified.

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**SCHEDULE 2.4**

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**SCHEDULE 3.4  
REGULATORY APPLICATIONS**

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**SCHEDULE 3.3.2  
THIRD PARTY AGREEMENTS**

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**SCHEDULE 4.1.2  
ISIS IMPROVEMENTS**

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**SCHEDULE 4.1.2  
HEPASENSE INTELLECTUAL PROPERT**

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**SCHEDULE 5.1  
RIGHTS RELATED TO SECURITIES  
AMENDMENTS TO THE FINANCE DOCUMENTS**

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IN WITNESS WHEREOF the Parties have executed this Agreement.

SIGNED

BY: /s/ KEVIN INSLEY

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for and on behalf of  
**Elan Corporation, plc**

SIGNED

BY: /s/ KEVIN INSLEY

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for and on behalf of  
**Elan Pharma International Limited**

SIGNED

BY: /s/ KEVIN INSLEY

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for and on behalf of  
**Elan International Services, Ltd.**

SIGNED

BY: /s/ B. LYNNE PARSHALL

\_\_\_\_\_  
for and on behalf of  
**Hepasense Limited**

SIGNED

BY: /s/ B. LYNNE PARSHALL

\_\_\_\_\_  
for and on behalf of  
**Isis Pharmaceuticals, Inc.**

#### QuickLinks

[TERMINATION AGREEMENT ELAN CORPORATION, PLC ELAN PHARMA INTERNATIONAL LIMITED ELAN INTERNATIONAL SERVICES, LTD. ISIS PHARMACEUTICALS, INC. AND HEPASENSE LTD](#)

**ISIS PHARMACEUTICALS AND ELAN CORPORATION CONCLUDE COLLABORATION IN  
HEPASense JOINT VENTURE AND RESTRUCTURE ORASENSE COLLABORATION**

*Isis Regains Rights to ISIS 14803 for HCV*

**CARLSBAD, CA, November 6, 2002**—Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has regained rights to ISIS 14803, in connection with the termination of its collaboration with Elan Corporation, plc. (NYSE: ELN) related to the HepaSense™ Ltd. joint venture. Additionally, Isis and Elan have agreed to amend the terms and extend their collaboration in the Orasense™ Ltd., joint venture through the end of 2002.

"We are pleased to have negotiated favorable outcomes to both of the joint ventures with Elan. Our partnerships with Elan have been highly productive, as we have leveraged the technology contributions and resources from both companies," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "We are enthusiastic about the potential of ISIS 14803 for patients with hepatitis C virus, and very happy to regain complete ownership of this drug. We will continue to aggressively pursue the clinical development of ISIS 14803. Our agreement to continue the Orasense joint venture is a validation of our exciting work to develop oral formulations of antisense drugs, with ISIS 104838 leading the way."

**HepaSense**

HepaSense is focused on the clinical development of the antisense drug ISIS 14803 for patients with Hepatitis C. The conclusion of Elan's participation in the collaboration results from Elan's continuing restructuring efforts. As part of the termination, all rights to ISIS 14803 have been returned to Isis, with a potential royalty due to HepaSense.

ISIS 14803 is an antisense inhibitor of the hepatitis C virus (HVC). Earlier this week, data presented from two Phase II studies demonstrated that ISIS 14803 is active in drug resistant, genotype 1 HCV patients, the most difficult-to-treat patient population. In the first trial, in which patients were dosed for one month, ISIS 14803 resulted in significant viral titer reductions. In a second ongoing trial, in which patients were dosed for three months, even more profound viral titer reductions were observed in six of 17 patients. The safety and efficacy of ISIS 14803 are being further evaluated in this ongoing 40 patient Phase II trial. Data from each of these trials were presented in November at the 53rd annual meeting of the American Association for the Study of Liver Diseases (AASLD) Monday.

**Orasense**

Orasense is a joint venture to develop an oral delivery platform for antisense drugs, and to develop an oral formulation of ISIS 104838, an antisense inhibitor of TNF-alpha, for the treatment of rheumatoid arthritis. The collaboration will continue through the remainder of this year, with Isis and Elan contributing funding according to ownership, 80.1 percent and 19.9 percent, respectively. In 2003, Elan will have the option to extend or conclude its participation in the Orasense collaboration.

In Orasense, multiple oral solid formulations of a second-generation antisense drug are being evaluated in Phase I clinical trials. Data from these trials will be presented at the 2002 annual meeting of the American Association of Pharmaceutical Scientists (AAPS) in November.

"Through our Orasense collaboration we have shown it is feasible to achieve oral systemic delivery of antisense oligonucleotides," stated Seamus Mulligan, Elan's Executive Vice President for Corporate Business Development. "This represents a major breakthrough in oral delivery of macromolecules. In addition, the agreements with Isis are important steps in Elan's restructuring efforts."

Isis will conduct a live webcast conference call to discuss this release and the Company's third quarter financial results today, Wednesday, November 6 at 8:30 a.m. Eastern time. To participate over the Internet go to [www.isispharm.com](http://www.isispharm.com) or to <http://www.firstcallevts.com/service/ajwz369610280gf12.html>. A replay of the webcast will be available at this address for up to 30 days.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene® (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline with two in late-stage development and six in Phase II human clinical trials. Affinitac™, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III trials for Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of more than 1,000 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

This press release contains forward-looking statements concerning the potential of ISIS 14803 and ISIS 104838 and the Orasense oral delivery technology. Any statement describing a goal, expectation, intention or belief of the Company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the company's Annual Report on Form 10-K and Quarterly Report on Form 10-Q for the periods ended December 31, 2001 and June 30, 2002, respectively, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other filings are available from the company.

HepaSense™ is a trademark of HepaSense, Ltd.

Orasense™ is a trademark of OraSense, Ltd.

Vitravene® is a registered trademark of Novartis AG.

GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc.

Affinitac™, a trademark of Eli Lilly and Company, is an investigational cancer compound being developed through an alliance between Lilly and Isis Pharmaceuticals, Inc. and marketed globally by Lilly.

