HORIZON PHARMA PLC

FORM 10-Q/A
(Amended Quarterly Report)

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q/A
(Amendment No. 2)

(MARK ONE)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended June 30, 2015

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____to _____

Commission File Number 001-35238

HORIZON PHARMA PUBLIC LIMITED COMPANY
(Exact name of registrant as specified in its charter)

Ireland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Connaught House, 1st Floor 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland	**Not Applicable**
(Address of principal executive offices)	**(Zip Code)**

011 353 1 772 2100
(Registrant's telephone number, including area code)

Not applicable
(Former name, former address and former fiscal year, if changed since last report)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act:

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Number of registrant's ordinary shares, nominal value $0.0001, outstanding as of August 3, 2015: 159,201,125.

EXPLANATORY NOTE

Horizon Pharma Public Limited Company (the "Company") is filing this Amendment No. 2 to Quarterly Report on Form 10-Q/A (this "Amendment") to amend the Company's Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2015, as filed with the Securities and Exchange Commission (the "SEC") on August 7, 2015 and as previously amended on November 6, 2015 (the "10-Q"). This Amendment is being filed solely to re-file a revised redacted version of Exhibit 10.8 to the 10-Q, reflecting changes to the Company's confidential treatment request with respect to certain portions of such exhibit. In addition, as required by Rule 12b-15 under the Securities Exchange Act of 1934, as amended, new certifications by the Company's principal executive officer and principal financial officer are filed as exhibits to this Amendment.

No attempt has been made in this Amendment to modify or update the other disclosures presented in the 10-Q. This Amendment does not reflect events occurring after the filing of the 10-Q or modify or update those disclosures that may be affected by subsequent events. Accordingly, this Amendment should be read in conjunction with the 10-Q and the registrant's other filings with the SEC.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

HORIZON PHARMA PLC

Date: May 26, 2017

By: /s/ Timothy P. Walbert

Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Date: May 26, 2017

By: /s/ Paul W. Hoelscher

Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)

INDEX TO EXHIBITS

Exhibit Number	Description of Document
10.8***	License Agreement, dated April 16, 1999, by and among Saul Brusilow, M.D., Brusilow Enterprises, Inc. and Medicis Pharmaceutical Corporation.
31.3	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.
31.4	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Exchange Act.

*** 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.

Exhibit 10.8

*****Text Omitted and Filed Separately with the Securities and Exchange Commission. Confidential Treatment Requested Under 17 C.F.R. Sections 200.80(b)(4) and 240.24b-2.**

LICENSE AGREEMENT

THIS LICENSE AGREEMENT (the "Agreement") is made and entered into as of April 16, 1999, among Saul W. Brusilow, M.D., an individual ("Brusilow") and Brusilow Enterprises, Inc., a Maryland corporation ("BEI"), as Licensors (collectively, "Licensors"), and Medicis Pharmaceutical Corporation, a corporation organized under the laws of Delaware, together with its Affiliates, as Licensee ("Licensee").

WITNESSETH :

WHEREAS, Licensors possess certain proprietary rights under patents relating to triglycerides and ethyl esters of phenylalkanoic acid and phenylalkanoic acid useful in the treatment of various disorders; and

WHEREAS, Licensee desires to obtain from Licensors, and Licensors desire to grant to Licensee, a license under Licensors' proprietary rights to research, develop, manufacture, market, sell and distribute the Licensed Products (as defined below);

NOW, THEREFORE, in consideration of the covenants, conditions, and undertakings hereinafter set forth, it is agreed by and among the parties as follows:

ARTICLE 1

DEFINITIONS

"Affiliate" shall mean, with respect to any Person, (i) any other Person of which securities or other ownership interests representing fifty percent (50%) or more of the voting interests are, at the time such determination is being made, owned, Controlled or held directly or indirectly, by such Person, or (ii) any other Person which, at the time such determination is being made, is Controlling, Controlled by or under common Control with, such Person. For the purposes hereof, "Control," whether used as a noun or verb, refers to the possession directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise.

"Agency" shall mean the United States Food and Drug Administration.

"Initial Licensed Product(s)" shall mean any product, the manufacture or sale of which would infringe upon any Valid Claim in any country where such product is manufactured, used or sold, and which is indicated for the treatment of urea cycle disorder.

"Legal Requirements" shall mean all laws, statutes, ordinances, codes, rules, regulations, published standards, permits, judgments, decrees, writs, injunctions, rulings, orders and other requirements of all Public Authorities.

"Licensed Know-How" shall mean any research and development information, inventions, know-how, pre-clinical, clinical and other technical data, in each case which are not generally known or available, which are owned, licensed or otherwise held by one or both of the Licensors or their respective Affiliates with the right to license or sublicense the same to Licensee during the term hereof and which are necessary or useful for the improving, making, using or selling of Licensed Products as provided in this Agreement.

"Licensed Product(s)" shall mean any Initial Licensed Product or Subsequent Licensed Product.

"Net Sales" shall mean the gross sales to Third Parties of any Licensed Product, less: (i) normal and customary rebates, trade discounts, and credits for returns and allowances, all to the extent actually allowed, (ii) sales or other excise taxes or duties imposed upon and paid by Licensee, or any of its Affiliates or sublicensees with respect to such sales, and (iii) transportation charges and insurance for transportation to the extent separately invoiced or separately reported on the invoice and paid by the seller. Notwithstanding the foregoing, Net Sales shall not include sales between or among Affiliates for resale by an Affiliate but shall include resales by Affiliates to Third Parties.

"Patent Rights" shall mean:

(a) all patents and patent applications owned or controlled by one or both Licensors or any of their respective Affiliates, or licensed to one or both Licensors (or any of their respective Affiliates) with rights to grant sublicenses thereunder, anywhere in the world at any time during the term hereof which are (i) listed on Schedule A, (ii) which are necessary or useful for the improvement, manufacture, use or sale of products for treating urea cycle disorder, or (iii) which derive from or are based upon the patents or patent applications described in clauses (i) or (ii) hereof and which are necessary or useful for the treatment of disease; and

(b) any improvement patents, reissues, confirmations, renewals, extensions, counterparts, divisions, continuations, continuations-in-part or patent-of-addition issued, assigned or licensed to one or both Licensors or their respective Affiliates of or relating to the patents or patent applications described in clause (a) hereof.

"Person" shall mean any natural person, corporation, firm, business trust, joint venture, association, organization, company, partnership or other business entity, or any government, or any agency or political subdivision thereof.

"Phase I Development" shall mean the development of a formulation of the Initial Licensed Product that has medically acceptable sensory and oral delivery characteristics.

"Public Authority" shall mean any supranational, national, regional, state or local government, court, governmental agency, authority, board, bureau, instrumentality or regulatory body.

"Subsequent Licensed Product(s)" shall mean any product, the manufacture, use or sale of which would infringe upon any Valid Claim in any country where such product is manufactured or sold, and which product is indicated for a disease other than, or in addition to, urea cycle disorder.

"Territory" shall mean all countries of the world.

"Third Party" means any Person which is not an Affiliate of any party hereto.

"Valid Claim" shall mean a claim of an issued and unexpired patent or pending patent application included within the Patent Rights in a country, which has not been held unenforceable,

unpatentable or invalid by a court or other governmental agency of competent jurisdiction from which no appeal can be or is taken, and which has not been specifically admitted to be invalid or unenforceable through reissue, disclaimer or otherwise.

ARTICLE 2

GRANT OF RIGHTS

2.1 License. Subject to the terms and conditions of this Agreement, Licensors hereby grant to Licensee a right and license, with the right to grant sublicenses, under the Patent Rights and Licensed Know-How to research, develop, make, have made, use, market, distribute, sell and have sold, the Licensed Products in the Territory, which right and license shall be exclusive, even as to Licensors.

2.2 Exclusivity. In order to assure Licensee of the exclusive rights granted in Section 2.1 hereof, Licensors shall not themselves use or grant to a Third Party any rights or licenses under the Patent Rights and Licensed Know-How to make, have made, use or sell anywhere in the Territory any Licensed Product. In addition, Licensors hereby agree (on their own behalf and on behalf of their Affiliates) to use all reasonable efforts to keep confidential all Licensed Know-How.

2.3 Sublicenses.

(a) The rights granted under Section 2.1 may be sublicensed by Licensee to any Person. In the event that Licensee desires to sublicense any rights granted under Section 2.1 to any Third Party, Licensee shall furnish to Licensors an executed copy of any such sublicense agreement.

(b) An sublicenses granted hereunder shall terminate upon termination of this Agreement; provided that upon expiration of this Agreement pursuant to Section 5.1 hereof, Licensee (or the applicable sublicensee) shall have a fully paid-up, royalty-free, non-cancelable license, subject (in the case of Licensee's sublicensees) to the terms of the applicable sublicense.

2.4 Disclosure of Technology. Upon the execution of this Agreement, and periodically thereafter as such information becomes available to Licensors, Licensors shall provide to Licensee copies of all available information and materials in tangible form within the Licensed Know-How or related to the Patent Rights.

2.5 Additional Technology. In the event that either Licensor or any of their respective Affiliates owns or controls (including under license with a right to grant sublicenses thereunder) any technology relating to (a) the elimination or excretion of waste nitrogen which is not licensed hereunder ("Related Technology"), or (b) the treatment of conditions that relate to other waste nitrogen disorders in respect of which no rights are licensed hereunder ("Complementary Technology" and, together with Related Technology, "New Technology"), Licensee shall have the right of first offer and last refusal to license the New Technology from such Licensor on the following terms:

Upon written request of Licensee, or in any event prior to offering rights to any New Technology to any Third Party, the applicable Licensor shall offer Licensee the right to obtain a license to such New Technology, by delivering to Licensee all data available to Licensors relating to the New Technology and its safety and efficacy together with a proposal for commercial terms, if available (the "Proposal"). Licensee shall have […***…] following receipt of the Proposal (the "Indication of Interest Notice Period") to

indicate whether or not it is interested in exercising an option to acquire a license under the New Technology which is the subject of the Proposal. If Licensee delivers written notice to Licensors stating that it wishes to consider exercising an option in respect of such New Technology (an "Indication of Interest"), then for a period of […***…] after receipt by the applicable Licensor of the Indication of Interest (the "Exclusive Negotiation Period"), the applicable Licensor shall negotiate in good faith exclusively with Licensee concerning the terms and conditions of a license in respect of the New Technology, and during the Exclusive Negotiation Period, the applicable Licensor shall take no other action in connection with the possible commercialization of the New Technology. The parties understand that, except as to financial terms, any license in respect of the New Technology shall contain terms and conditions substantially similar to those contained in this Agreement. In the event that (i) Licensee fails to deliver an Indication of Interest within the Indication of Interest Notice Period, or (ii) the parties, each acting in good faith and in a timely fashion, fail to execute a license agreement with respect to such New Technology within the Exclusive Negotiation Period, then in either case the applicable Licensor shall be free to proceed with the Proposal without further obligation to Licensee with respect to such New Technology; provided , that (1) neither Licensor may offer a license to such New Technology on terms and conditions which are more favorable to a Third Party than those offered to Licensee, and (2) in the event that a Third Party is willing to provide consideration to the applicable Licensor which is both superior in value to that offered by Licensee and acceptable to the applicable Licensor, such Licensor shall, promptly upon receipt of such Third Party proposal, give Licensee written notice of the terms and conditions thereof, together with any additional information relating to the New Technology which may have arisen since the Proposal ("Second Notice"), and for a period of […***…] following receipt of the Second Notice, Licensee shall have the right, in its sole discretion ("Right of Last Refusal"), to match such Third Party proposal; provided that if Licensee wishes to exercise its Right of Last Refusal to any Complementary Technology, Licensee shall exercise such right only upon payment to the Licensors of US$[…***…] (in the aggregate) for each license of Complementary Technology offered in a Second Notice. If Licensee shall fail to exercise the Right of Last Refusal with respect to any New Technology, the applicable Licensor shall be free to proceed with the Proposal relating to such New Technology on such terms without further obligation to Licensee with respect to such New Technology. In the event that […***…] exercises its right to assume ownership of any New Technology developed by Brusilow pursuant to Brusilow's existing agreements with […***…], Brusilow agrees to use his reasonable best efforts to cause […***…] to offer a license to such New Technology to Licensee. Each Licensor agrees not to enter into any agreement which would interfere with or preclude the exercise of the rights granted to Licensee hereunder in respect of New Technology.

ARTICLE 3

COMPENSATION TERMS

3.1 License Fee . Upon the execution of this Agreement and in consideration of the licenses granted hereunder, Licensee shall pay to Licensors a license fee of […***…] United States dollars (US$[…***…]).

3.2 Milestone Fees .

(a) Upon […***…], Licensee shall pay to Licensors […***…] United States dollars (US$[…***…]) within […***…] following such […***…].

(b) Upon […***…], Licensee shall pay to Licensors […***…] United States dollars (US$[…***…]) within […***…] following the […***…].

3.3 Royalties .

(a) Licensee shall pay Licensors a royalty on […***…] Net Sales of Initial Licensed Products by Licensee, its Affiliates and sublicensees, as follows:

(i) On Net Sales of each Initial Licensed Product in respect of which […***…], a royalty rate of […***…] percent ([…***…]%) shall be payable; and

(ii) On Net Sales of each Initial Licensed Product in respect of which […***…], a royalty rate of […***…] percent ([…***…]%) shall be payable.

(b) Licensee shall pay Licensors a royalty equal to […***…] percent ([…***…]%) of annual Net Sales of Subsequent Licensed Products by Licensee, its Affiliates and sublicensees.

(c) Royalties payable by Licensee in any particular […***…] shall be calculated as follows:

(i) Licensee shall determine Net Sales of Licensed Products for such […***…] on a product-by-product basis.

(ii) Licensee shall apply the royalty rates set forth in paragraphs (a) and (b) above to Net Sales of each Licensed Product.

3.4 Certain Expenses . With regard to out-of-pocket expenses associated with the preparation, filing, prosecution and maintenance of all patent applications within the Patent Rights and related development costs actually incurred by Licensors prior to the effective date of this Agreement ("Sunk Patent Costs"), Licensee shall pay to Licensors, as an additional royalty within […***…] of Licensors' submission of a statement and a request for payment to Licensee, together with invoices, receipts or other suitable supporting documentation for each expense set forth on such statement, an amount equal to such Sunk Patent Costs, up to a maximum of US$[…***…].

3.5 Single Royalty; Non-Royalty Sales . It is understood that in no event shall more than one royalty be payable under this Article 3 with respect to a particular unit of Licensed Product. No royalty shall be payable with respect to sales of Licensed Products by Licensee, its Affiliates and sublicensees in any country in which Licensors do not own, control or have a license under (with the right to sublicense) any Patent Rights. No royalty shall be payable under this Article 3 with respect to sales of Licensed Products among Licensee and its Affiliates, or among sublicensees and their Affiliates, but a royalty shall be due upon the subsequent sale of the Licensed Product to a Third Party. No royalty shall be payable for (i) Licensed Product used in clinical trials, (ii) Licensed Product used by Licensee, its Affiliates or sublicensees for research, or (iii) customary quantities of Licensed Product distributed as free samples. In the event that a single Licensed Product has multiple indications, if one of the indications is for urea cycle disorder, such Licensed Product shall constitute an Initial Licensed Product. All royalties and payments described in this Article 3 are aggregate payments. Royalties and payments payable by Licensee pursuant to Article 3 shall be allocated between Licensors as follows: (A) the license fee under Section 3.1 shall be allocated with US$[...***...] attributable to BEI and US$[...***...] attributable to Brusilow; (B) the milestone fees under Section 3.2(a) shall be allocated with US$[...***...] attributable to BEI and US$[...***...] attributable to Brusilow; (C) the milestone fees under Section 3.2(b) shall be allocated with US$[...***...] attributable to BEI and US$[...***...] attributable to Brusilow; and (D) all royalties under Section 3.3 shall be allocated with [...***...] percent ([...***...]%) attributable to BEI and [...***...] percent ([...***...]%) attributable to Brusilow.

ARTICLE 4

CERTAIN OBLIGATIONS OF LICENSORS

4.1 Services and Obligations of Licensors. Brusilow and/or BEI, as the case may be, will provide services and render assistance to Licensee as follows:

(a) Licensee understands and agrees that Brusilow is presently a Professor Emeritus of Johns Hopkins University and the parties intend that he shall continue in such capacity subsequent to the consummation of the transactions contemplated by this Agreement, subject to compliance with the terms of this Agreement. Brusilow agrees that he will make himself available to consult with an independent contract research organization ("CRO") selected by Licensors and assigned to the task of developing the Patent Rights and obtaining Agency approval for use of Initial Licensed Products and Subsequent Licensed Products. Brusilow will provide the following scope of services to the CRO: (i) consultation in connection with medical, pharmacological and other scientific aspects of the Patent Rights; and (ii) consultation in connection with obtaining Agency approval of the use of the Initial Products and the Subsequent Licensed Products. Brusilow's undertakings under this Section 4.1(a) shall be limited to […***…] per […***…]. Brusilow shall be compensated by the CRO at the rate of not less than $[…***…] per […***…] for services rendered under this Section 4.1(a).

(b) In addition, Brusilow shall provide all assistance that Licensee deems necessary or desirable to prosecute and defend the Patent Rights. In the event that Licensee requests such assistance from Brusilow, Brusilow shall be compensated by Licensee at the rate of not less than $[…***…] per […***…] for services rendered under this Section 4.1(b), subject to Section 6.3 hereof.

(c) Licensors shall execute all documents as may be needed to perfect Licensee's rights under this Agreement.

(d) Immediately following execution hereof, Brusilow agrees to convey to Licensee (or its designee) any and all orphan drug designations which he holds relating to sodium phenylbutyrate. Such transfer shall be for […***…] consideration (US$[…***…]), and shall be pursuant to a transfer agreement, substantially in the form attached hereto as Exhibit I.

ARTICLE 5

TERM AND TERMINATION

5.1 Term. This Agreement shall become effective as of the date hereof and, unless earlier terminated pursuant to the other provisions of this Article 5, shall continue in full force and effect until the later of (a) the last to expire of the Patent Rights for any Licensed Product or (b) ten (10) years from the date of this Agreement (the "Term"). Except in the event of termination of the Term of this Agreement under Section 5.2 or 5.3, upon the expiration of the Term of this license, Licensee will have a fully paid, royalty-free, freely sublicensable license to research, develop, make, have made, use, market, distribute, sell and have sold, the Licensed Products in the Territory, and Licensee shall have no further payment obligation to Licensors, other than in respect of any amounts which accrued prior to the expiration of the Term and remain unpaid.

5.2 Termination for Breach . In the event of a material breach of this Agreement (including the breach of a representation or warranty), which breach is not cured within […***…] after written notice is given by the non-breaching party to the breaching party specifying the breach, the non-breaching party, in addition to any other remedy which it may have, shall be entitled to terminate this Agreement forthwith.

5.3 Termination by Licensee . Any provision herein notwithstanding, Licensee may terminate this Agreement at any time by giving Licensors at least […***…]' prior written notice. In the event of a termination pursuant to this Section 5.3, all rights granted herein to Licensee shall forthwith revert to Licensors.

5.4 Rights on Termination .

(a) Termination of this Agreement for any reason shall not release either party hereto from any liability which at the time of such termination has already accrued to the other party.

(b) In the event that this Agreement is terminated due to a breach by either Licensor and subject to the terms of any Third Party Agreement, (i) Licensee shall be free to sell all Licensed Products in its inventory (including all work-in-process) and (ii) Licensee shall have the rights set forth in Section 8.3 in respect of such breach.

(c) In the event that this Agreement is terminated due to a breach by Licensee, (i) all licenses granted hereunder shall terminate, (ii) subject to Article 7 hereof, any Licensed Know-How provided to Licensee in written form shall be promptly returned to Licensors or destroyed, at Licensors' option and (iii) Licensors shall have the rights set forth in Section 8.3 in respect of such breach.

(d) Articles 7 and 11, and Sections 2.3, 5.1, 5.4, 5.5, 8.3, 10.3 and 10.4, shall survive the expiration and any termination of this Agreement. Except as otherwise provided in this Section 5.4(d), all rights and obligations of the parties under this Agreement shall terminate upon the expiration or termination of this Agreement.

5.5 Further Licensee Agreement Upon Termination . In the event that Licensee's rights and licenses under this Agreement are terminated, Licensee agrees not to make, use or sell Licensed Products, or use in any manner the Licensed Know-How, for so long as such manufacture, use or sale would infringe upon any Valid Claim of Patent Rights.

5.6 Termination Upon Bankruptcy . Licensee or Licensors may terminate this Agreement upon written notice to the other party if the other party makes a general assignment for the benefit of creditors, is the subject of proceedings in voluntary or involuntary bankruptcy or has a receiver or trustee appointed for substantially all of its property; provided that in the case of an involuntary bankruptcy proceeding such right to terminate shall only become effective if the other party consents thereto or such proceeding is not dismissed within […***…] after the filing thereof. Each of the parties hereto acknowledges and agrees that this Agreement (i) constitutes a license of Intellectual Property (as such term is defined in the United States Bankruptcy Code, as amended (the "Code")), and (ii) is an executory contract, with significant obligations to be performed by each party hereto. The parties agree that Licensee may fully exercise all of its rights and elections under the Code, including, without limitation, those set forth in Section 365(n) of the Code. The parties further agree that, in the event that Licensee elects to retain its rights as a licensee under the Code, Licensee shall be entitled to complete access to any technology licensed to it hereunder and all embodiments of such technology. Such embodiments of the

technology shall be delivered to Licensee not later than (x) […***…], or (y) if not delivered under (x) above, […***…].

ARTICLE 6

PATENTS AND INFRINGEMENTS

6.1 Pursuit and Maintenance of Patent Rights . Licensee shall, at its own expense, file, prosecute and maintain Patent Rights in those countries of the Territory set forth on Schedule C hereto, and in accordance with the time schedule therefor set forth in Schedule C . Licensee agrees to keep Licensors reasonably informed as to the status of the Patent Rights in the Territory. Except as provided in Section 4.1 hereof, Licensors shall have no obligation to make any payments that are not reimbursed by Licensee in connection with filing, prosecuting and maintaining the Patent Rights.

6.2 Notice of Infringement . Each party shall promptly notify the other of any conflicting use or any act of infringement or appropriation of any Patent Right by unauthorized Persons which comes to its attention; provided that Licensors will not notify a Third Party of the infringement of any Patent Rights without first obtaining the written consent of Licensee.

6.3 Enforcement and Defense .

(a) Subject to the limitations described in this Section 6.3, Licensee shall, at its own expense, have the right but not the obligation to engage in proceedings involving infringement or appropriation of any Patent Right and to name Licensors as parties in such proceedings. Licensee shall have the right to take such steps as it deems necessary in order to terminate such infringement or appropriation, and may settle any dispute with any Third Party at any time regarding such infringements and appropriations; provided that Licensee shall not have the right to settle, compromise or take any action in such litigation which diminishes, limits or inhibits the scope, validity or enforceability of the Patent Rights without the express written consent of Licensors. In the event that Licensee exercises its rights under this Section 6.3, Licensee agrees to keep Licensors fully informed of all developments in connection with any settlements and negotiations and to consult with Licensors prior to making any final settlement, consent judgment or other voluntary disposition of the matter. The value of any recovery actually received by Licensee in connection with any litigation, arbitration or settlement under this Section 6.3(a), net of any reasonable expenses or costs incurred by Licensee in obtaining such recovery (including, without limitation, reasonable legal and expert fees), shall be […***…]; provided, that […***…].

(b) If Licensee does not wish to take or continue any action to terminate such infringement or appropriation, Licensors shall have the right to engage in negotiations and proceedings involving infringement or appropriation of any Patent Right solely at its own expense; provided that it keeps Licensee fully informed of the progress of such negotiations and proceedings and consults with Licensee and obtains Licensee's written consent, which consent shall not be unreasonably withheld, prior to making any final settlement, consent judgment or other voluntary disposition of the matter. Each party agrees to cooperate with the other to the fullest extent possible with respect to any negotiations or proceedings under this Section 6.3.

6.4 Patent Term Restoration .

(a) Licensee shall notify Licensors of (i) the issuance of each United States patent included within the Patent Rights, giving the date of issue and patent number for each such

patent and (ii) each notice pertaining to any patent included within the Patent Rights which it receives as patent owner pursuant to the United States Drug Price Competition and Patent Term Restoration Act of 1984 (the "Act"), including notices pursuant to Sections 101 and 103 of the Act from Persons who have filed an abbreviated NDA. Such notices shall be given promptly, but in any event within […***…] of each such patent's date of issue or receipt of each such notice pursuant to the Act, whichever is applicable. Licensee shall notify Licensors of each filing for patent term restoration under the Act, any allegations of failure to show due diligence and all awards of patent term restoration (extensions) with respect to the Patent Rights.

(b) Likewise, Licensors or Licensee, as the case may be, shall inform the other party of patent extensions and periods of data exclusivity in the rest of the world regarding any Licensed Products and more generally the parties shall diligently cooperate with respect to any procedures for patent and period of data exclusivity extensions, such as but not limited to, Supplementary Protection Certificates, the above-mentioned patent term restoration and corresponding GATT regulations.

ARTICLE 7

CONFIDENTIALITY

7.1 Confidential Information . Except as expressly set forth in this Article 7, each party shall, and shall cause its Affiliates and its and their respective officers, directors, employees, agents and subcontractors (collectively, "Representatives") to, keep confidential any and all technical, commercial, scientific and other proprietary data, processes, documents or other information (whether in oral, written or electronic form) or physical object (including, without limitation, intellectual property, marketing data, agreements between any party and a third party, license applications, and business plans and projections of any party) acquired from the other party, its Affiliates or any of their respective Representatives in respect of the transactions contemplated by this Agreement and which relate (in the case of a party) to the other party or any of its Affiliates or their respective businesses or products ("Confidential Information"), and each party shall not disclose directly or indirectly, and shall cause its respective Affiliates and Representatives not to disclose directly or indirectly, any Confidential Information to anyone outside such Person, such Affiliates and their respective Representatives, except that the foregoing restriction shall not apply to any information disclosed hereunder to any party if such Person (the "Receiving Person") can demonstrate that such Confidential Information:

(a) is or hereafter becomes generally available to the trade or public other than by reason of any breach hereof;

(b) was already known to the Receiving Person or such Affiliate or Representative as shown by written records;

(c) is disclosed to the Receiving Person or such Affiliate or Representative by a third party who has the right to disclose such information;

(d) is developed by or on behalf of the Receiving Person or any of its Affiliates independently, without reliance on Confidential Information received hereunder; or

(e) based on such Person's good faith judgment with the advice of counsel, is otherwise required to be disclosed in compliance with applicable Legal Requirements by a Public

Authority and such information shall remain Confidential Information for all other purposes unless subparagraphs (a) through (d) above otherwise apply.

7.2 Use of Confidential Information. Except in furtherance of their respective rights and obligations hereunder, each party agrees that it shall not (and shall not permit any of its Affiliates to) at any time use any Confidential Information in the conduct of its businesses without the prior written consent of the other party. The obligations set forth in this Article 7 shall extend to copies, if any, of Confidential Information made by any of the Persons referred to in Section 7.1 and to documents prepared by such Persons which embody or contain Confidential Information, and to any electronic data files containing Confidential Information.

7.3 Protection of Confidential Information. Each party shall deal with Confidential Information so as to protect it from disclosure with a degree of care not less than that used by it in dealing with its own information intended to remain exclusively within its knowledge and shall take reasonable steps to minimize the risk of disclosure of Confidential Information.

7.4 Survival of Obligations. The obligations set forth in this Article 7 shall survive the expiration, termination or assignment of this Agreement for a period of […***…].

7.5 Return of Confidential Information. Within […***…] after the termination of this Agreement, the Receiving Person shall (and shall cause its Affiliates and Representatives to), at the option of the Person making disclosure (the "Disclosing Person"), return to the Disclosing Person or destroy all Confidential Information in its or their possession; provided, however, that the Receiving Person may, upon notice to the Disclosing Person, retain in its legal files or in the office of outside legal counsel one copy of any document solely for use in any pending legal proceeding to which such document relates. Such notice shall set forth, in reasonable detail, a list of the documents so retained.

ARTICLE 8

REPRESENTATIONS, WARRANTIES AND COVENANTS

8.1 Representations and Warranties of Licensee.

(a) Licensee is a corporation duly incorporated and validly existing and in good standing under the laws of the State of Delaware, with the corporate power to own, lease and operate its properties and to carry on its business as now conducted.

(b) Licensee has all necessary corporate power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

(c) The execution, delivery and performance of this Agreement by Licensee does not conflict with or contravene the certificate of incorporation or by-laws of Licensee, nor will the execution, delivery or performance of this Agreement conflict with or result in a breach of, or entitle any party thereto to terminate, any material agreement or instrument to which Licensee is a party, or by which any of its assets or properties is bound.

(d) This Agreement has been duly authorized, executed and delivered by Licensee and constitutes a legal, valid and binding agreement of Licensee, enforceable against Licensee in accordance with its terms, except as enforceability may be limited by bankruptcy, insolvency, moratorium, reorganization or other similar laws affecting creditors' rights generally.

8.2 Representations, Warranties and Covenants of Licensors .

(a) BEI is a corporation duly incorporated and validly existing as a corporation and in good standing under the laws of Maryland, with the corporate power to own, lease and operate its properties and to carry on its business as now conducted.

(b) BEI has all necessary corporate power and authority to enter into this Agreement and to consummate the transactions contemplated hereby.

(c) The execution, delivery and performance of this Agreement by BEI does not conflict with or contravene its articles or certificate of incorporation or by-laws, nor will the execution, delivery or performance of this Agreement by either Licensor conflict with or result in a breach of, or entitle any party thereto to terminate, any material agreement or instrument to which either Licensor is a party, or by which any of any of their respective assets or properties is bound. No Third Party has any right, title or interest in or to the Patent Rights or the Licensed Know-How, including, without limitation, Johns Hopkins University or its Affiliates. Licensors have provided to Licensee a true, complete and correct copy of every agreement between either Licensor or its/his Affiliates, on the one hand, and Johns Hopkins University or its Affiliates, on the other hand, which relates to or could affect either Licensor's right, title or interest in the Patent Rights or Licensed Know-How (including any amendments thereto), and all such agreements are listed on Schedule B hereto. Licensors have carried out all requirements under each such agreement necessary to enable each Licensor to grant the license granted to Licensee hereunder, and there are no other requirements necessary for either Licensor to grant such license. All such agreements are in full force and effect, and neither Licensor has received nor delivered any notice of default thereunder. There are no circumstances known to either Licensor which, with notice or lapse of time or both, could result in a default under any of such agreements.

(d) This Agreement has been duly authorized, executed and delivered by Licensors and constitutes a legal, valid and binding agreement of Licensors, enforceable against Licensors in accordance with its terms, except as enforceability may be limited by bankruptcy, insolvency, moratorium, reorganization or other similar laws affecting creditors' rights generally.

(e) All Patent Rights have been registered in, filed in or issued by the appropriate patent offices of each jurisdiction listed on Schedule A hereto, and in each case is currently in effect and all maintenance fees and renewals thereof have been duly made with respect thereto. Licensors own or have full and exclusive rights to use and exploit under licenses (and to license or sublicense) all their rights under the Patent Rights and Licensed Know-How. The Patent Rights are not encumbered in any way, such as by claims, liens, mortgages or security interests (perfected or otherwise). There have been no material claims made against either Licensor asserting the invalidity or unenforceability of, or with respect to the Patent Rights, the misuse of, the Patent Rights or Licensed Know-How, nor is either Licensor aware that any such claims exist. Neither Licensor has received a notice of conflict of the Patent Rights or Licensed Know-How with the asserted rights of others, or otherwise challenging their rights to use any of the Patent Rights or Licensed Know-How. None of the rights of either Licensor under the Patent Rights or Licensed Know-How will be adversely affected by the execution, delivery or performance of this Agreement, or the consummation of the transactions contemplated herein. Licensors have taken all action reasonably necessary, using its current standard business practices, to protect the Patent Rights and Licensed Know-How.

(f) EXCEPT AS SET FORTH IN PARAGRAPHS (a) THROUGH (e) OF THIS SECTION 8.2, LICENSORS MAKE NO WARRANTIES, EXPRESS OR IMPLIED, OF

MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OF ANY SUBJECT MATTER DEFINED IN THE CLAIMS OF THE PATENT RIGHTS OR TANGIBLE MATERIALS RELATED THERETO.

8.3 Indemnification .

(a) Indemnity by Licensee . Licensee hereby agrees to indemnify, defend and hold harmless Licensors, their Affiliates, officers, directors, employees and agents from and against any liabilities, claims, damages, costs, expenses (including reasonable attorneys' fees), judgments (collectively, "Damages") arising out of, based upon or resulting from (i) the development, manufacture, sale or use of any Licensed Product, or (ii) a breach of this Agreement (including the breach of a representation or warranty) by Licensee, except to the extent that in either case any such Damages arise out of, are based upon or result from (A) a breach of this Agreement (including the breach of a representation or warranty) by either Licensor, or (B) the negligence or willful misconduct of either Licensor.

(b) Indemnity by Licensors . Licensors hereby agree, jointly and severally, to indemnify, defend and hold harmless Licensee, its Affiliates, sublicensees, officers, directors, employees and agents from and against any Damages arising out of, based upon or resulting from (i) a breach of this Agreement (including the breach of a representation or warranty) by either Licensor, or (ii) the negligence or willful misconduct of either Licensor; provided , however , that the liability of each Licensor under this Section 8.3(b) shall be limited to [...***...]; provided , further , that in the event that Licensee, its Affiliates, sublicensees, officers, directors, employees or agents shall have any Damages in excess of [...***...], as of the date that such Licensor's liability for such Damages has been determined, Licensee shall have the right to [...***...].

(c) Indemnification Procedures .

(i) Any party entitled to indemnification under paragraph (a) or (b) of this Section 8.3 (an "Indemnified Party") shall promptly notify the party potentially responsible for such indemnification (the "Indemnifying Party") upon becoming aware of any claim or claims asserted or threatened against such Indemnified Party which could give rise to a right of indemnification under this Agreement; provided , however , that the failure to give such notice shall not relieve the Indemnifying Party of its indemnity obligation hereunder except to the extent that such failure substantially prejudices its rights hereunder.

(ii) The Indemnifying Party shall have the right to defend, at its sole cost and expense, such claim by all appropriate proceedings, which proceedings shall be prosecuted diligently by the Indemnifying Party to a final conclusion or settled at the discretion of the Indemnifying Party; provided , however , that the Indemnifying Party may not enter into any compromise or settlement unless (A) the Indemnified Party consents thereto, which consent shall not be unreasonably withheld, and (B) such compromise or settlement includes as an unconditional term thereof, the giving by each claimant or plaintiff to the Indemnified Party of a release from all liability in respect of such claim.

(iii) The Indemnified Party may participate in, but not control, any defense or settlement of any claim controlled by the Indemnifying Party pursuant to this Section 8.3 and shall bear its own costs and expenses with respect to such participation; provided , however , that the Indemnifying Party shall bear such costs and expenses if counsel for the Indemnifying Party shall have reasonably determined that such counsel may not properly represent both the Indemnifying Party and the Indemnified Party.

(iv) If the Indemnifying Party fails to notify the Indemnified Party within [...***...] after receipt of notice of a claim in accordance with Section 8.3(c)(i) hereof that it elects to defend the Indemnified Party pursuant to this Section 8.3(c), or if the Indemnifying Party elects to defend the Indemnified Party but fails to prosecute or settle the claim diligently and promptly, then the Indemnified Party shall have the right to defend, at the sole cost and expense of the Indemnifying Party, the claim by all appropriate proceedings, which proceedings shall be promptly and vigorously prosecuted by the Indemnified Party to a final conclusion or settled; provided , however , that in no event shall the Indemnifying Party be required to indemnify the Indemnified Party for any amount paid or payable by the Indemnified Party in the settlement of any such claim agreed to without the consent of the Indemnifying Party, which shall not be unreasonably withheld.

ARTICLE 9

DUE DILIGENCE

9.1 General . Licensee shall use commercially reasonable efforts to register, market and sell and to continue to market and sell the Initial Licensed Product in the United States. Without in any way limiting the generality of the foregoing, Licensee agrees to use commercially reasonable efforts to accomplish […***…] and shall be required to spend up to US$[…***…] to complete […***…]. Licensee shall use commercially reasonable efforts to register, market and sell and to continue to market and sell any Subsequent Licensed Product(s). Upon a failure by Licensee to meet its obligations under this Section 9.1 with respect to any Licensed Product, Licensors shall have the right, upon […***…]' written notice to Licensee, to terminate Licensee's right to manufacture or have manufactured and/or market such Licensed Product. Upon any such termination, the rights granted hereunder with respect to such Licensed Product in such country or countries shall revert to Licensors. Licensors shall use commercially reasonable efforts to support externally-sponsored research concerning the use of phenylbutyrate and the technology embodied in the Patent Rights.

9.2 Development Plan; Semi-Annual Reports . Following execution hereof, Licensee agrees to provide to Licensors with its then-current development plan for the Licensed Products, and to provide updated development plans to Licensors as such plans become available. The parties agree that all such development plans shall constitute Confidential Information of Licensee. In addition, at least […***…] every […***…] prior to first commercial sale of a Licensed Product, Licensee agrees to provide to a representative of Licensors upon request (i) a report, which may be oral or written, of its progress to such date with respect to the development and commercialization of the Licensed Products, and (ii) an opportunity to discuss with representatives of Licensee Licensee's progress toward first commercial sale of Licensed Products.

9.3 Option to Extend License . In the event that Licensee has neither (i) filed an NDA with the Agency on or before [...***...], or (ii) made its first commercial sale of a Licensed Product on or before [...***...], Licensee shall have the right, at its sole option, to either (a) commence making aggregate [...***...] royalty payments to Licensors of US$[...***...] for the [...***...] period beginning [...***...], and US$[...***...] for each successive [...***...] period thereafter ("Extension Payments"), and thereby maintain its rights under this Agreement, or (b) terminate this Agreement and deliver to Licensors all research and development information, know-how, pre-clinical, clinical and other technical data it has developed in connection with

the development of Licensed Products. Licensee's right to terminate this Agreement may be exercised at any time, regardless of whether Licensee has previously made any Extension Payment.

9.4 Notification. Licensee shall promptly notify Licensors in writing if at any time Licensee does not intend to continue to obtain regulatory approval for and/or market and sell any Licensed Product. Upon delivery by Licensee of such a notice, the rights and licenses granted to Licensee hereunder with respect to such Licensed Product shall terminate and shall revert to Licensors.

ARTICLE 10

ACCOUNTING AND RECORDS

10.1 Reports. Beginning with […***…] ending […***…], Licensee shall provide […***…] written reports to Licensors within […***…] after the end of […***…] during the Term of this Agreement, stating in each such report in the case of Licensed Products, the number, description, and aggregate Net Sales of Licensed Products sold during the […***…] and upon which a royalty is payable under Article 3 above or, if Licensee has opted to make Extension Payments (or royalties are not otherwise due for such period), the written report shall so state. The royalty report shall be certified as correct by an authorized officer of Licensee and shall include a reasonably detailed description of all deductions from gross sales made to determine Net Sales. In the event that Licensee sublicenses any of the rights licensed by Licensors hereunder, Licensee shall provide Licensors with copies of any reports it receives from its sublicensees which may be pertinent to royalty accounting hereunder.

10.2 Payment. […***…] the making of each such report of Section 10.1, Licensee shall pay to Licensors the royalties at the rate specified in Section 3.3, if any such royalties are due. All payments by Licensee to Licensors hereunder shall be made in United States dollars. If any currency conversion shall be required in connection with the calculation of royalties or the payment of other compensation hereunder, such conversion shall be made by using the rate of exchange published in The Wall Street Journal for the last business day of the applicable calendar quarter. The parties hereto agree that Licensee's failure to pay royalties when due shall constitute a material breach of this Agreement.

10.3 Withholding Taxes. Any withholding or other taxes that Licensee or any of its Affiliates are required by law to withhold and pay on behalf of Licensors with respect to the royalties payable to Licensors under this Agreement shall be deducted from such royalties and other compensation and paid contemporaneously with the remittance to Licensors; provided, however, that in regard to any tax so deducted Licensee shall furnish Licensors with proper evidence of the taxes paid on its behalf. Licensors will furnish Licensee with appropriate documents to secure application of the favorable rate of withholding tax under applicable tax treaties.

10.4 Records; Inspection.

(a) Licensee shall keep complete, true and accurate books of account and records for the purpose of determining the amounts payable to Licensors under this Agreement. Such books and records shall be kept at Licensee's principal place of business for at least [...***...] following the end of [...***...] to which they pertain, and will be open for inspection during such [...***...] period by a "Big Five" independent public accountant not providing accounting services to Licensors, Licensee or any of their respective Affiliates, which is reasonably acceptable to both parties, for the purpose of verifying Licensee's [...***...] written reports. Such inspections may be made no more than [...***...] each calendar year, during normal business hours and upon [...***...]' prior notice. Such accountant shall be permitted access only to the books and records which Licensee

determines are necessary for verifying the […***…] written reports. Any such information shall be considered to be Confidential Information of Licensee.

(b) Inspections conducted under this Section 10.4 shall be at the expense of […***…], unless an underpayment exceeding […***…] percent ([…***…]%) of the amount paid for the period covered by the inspection is established in the course of any such inspection, whereupon all costs relating thereto will be paid by […***…], as well as any unpaid royalties due and owing to Licensors within the […***…] after the notification by […***…] to […***…] that an underpayment has been discovered.

ARTICLE 11

MISCELLANEOUS

11.1 Publicity. Licensee and Licensors shall cooperate in the preparation of a mutually-agreeable press release and other publicity disclosing the existence of this Agreement and their business relationship. Except for the information disclosed in such press release or publicity, neither Licensee nor Licensors shall disclose the existence or any terms of this Agreement without the prior written consent of the other party (which consent shall not be unreasonably withheld), except for such limited disclosure as may be reasonably necessary to either party's bankers, investors, attorneys or other professional advisors, or in connection with a merger or acquisition, or as may be required by law in the offering of securities or in securities regulatory filings or otherwise.

11.2 Waiver. It is agreed that no waiver by any party hereto of any breach or default of any of the covenants or agreements herein set forth shall be deemed a waiver as to any subsequent and/or similar breach or default.

11.3 Independent Contractors. The relationship of the parties hereto is that of independent contractors. None of Licensors or Licensee hereto is an agent, partner or joint venturer of the other for any purpose.

11.4 Notices. Any notice required or permitted to be given to the parties hereto shall be deemed to have been properly given if delivered in person or when received if mailed by first class certified mail or sent by facsimile to the other party at the address or facsimile number, as applicable, indicated below or to such other addresses or facsimile numbers as may be designated in writing by the parties from time to time during the term of this Agreement. Licensors agree that notice to BEI shall constitute notice to Licensors for all purposes hereunder.

BEI:

Brusilow Enterprises, Inc.
4804 Keswick Road
Baltimore, Maryland 21210
Attention: Saul W. Brusilow, M.D.
Telephone:
Facsimile:

with a copy to:

Thomsen and Burke LLP
One North Charles Street
Suite 400
Baltimore, Maryland 21201
Attention: John B. Ward, Jr.
Telephone: (410) 539-2595

Facsimile: (410) 783-0710

Licensee:

Medicis Pharmaceutical Corporation
4343 East Camelback Road
Suite 250
Phoenix, Arizona 85018-2700
Attention: Jin Sun Kim, Esq.
Telephone: (602) 808-8800
Facsimile: (602) 808-3874

with a copy to:

Akin, Gump, Strauss, Hauer & Feld, L.L.P.
590 Madison Avenue
New York, New York 10022
Attention: L. Kevin O'Mara, Jr., Esq.
Telephone: (212) 872-1000
Facsimile: (212) 872-1002

11.5 Complete Agreement. It is understood and agreed among the parties that this Agreement constitutes the entire agreement with respect to the subject matter of this Agreement, both written and oral, among the parties, and that all prior agreements respecting the subject matter hereof, either written or oral, expressed or implied, shall be abrogated, canceled, and are null and void and of no effect, unless such other agreement, by its written terms, is an exception to this provision. No amendment or change hereof or addition hereto shall be effective or binding on any of the parties hereto unless reduced to writing and executed by the respective duly authorized representatives of each of the parties hereto.

11.6 Severability. In the event that any provision of this Agreement becomes or is declared by a court of competent jurisdiction to be illegal, unenforceable or void, this Agreement shall continue in full force and effect without said provision and the parties shall exert their best efforts to amend this Agreement to include a provision which is valid, legal and enforceable and which carries out the original intent of the parties.

11.7 Counterparts and Headings. This Agreement may be executed in counterparts, each of which shall be deemed to be an original and both together shall be deemed to be one and the same agreement. All headings are inserted for convenience of reference only and shall not affect its meaning or interpretation.

11.8 Governing Law. All matters affecting the interpretation, validity and performance under this Agreement shall be governed by the internal laws of the State of Delaware, without regard for its conflict of laws principles.

11.9 Force Majeure. No party shall be liable to the other, or be in default under the terms of this Agreement, for its failure to fulfill its obligations hereunder to the extent such failure arises for any reason beyond its control including, without limitation, strikes, lockouts, labor disputes, acts of God, acts of nature, acts of governments or their agencies, fire, flood, storm, power shortages or power failure, war, sabotage, inability to obtain sufficient labor, raw materials, fuel or utilities, or inability to obtain transportation (each, an "Event of Force Majeure"); provided that the party relying on the provisions of this Section 11.9 shall forthwith give to the other notice of its inability to observe or perform the provisions of this Agreement and the reasons therefor; and provided further that the suspension of the

obligations of the party so affected will continue only for so long as such Event of Force Majeure continues.

11.10 Adverse Experience Reporting. During the Term, each party shall notify the other immediately of any information (howsoever obtained and from whatever source) concerning any unexpected side effect, injury, toxicity or sensitivity reaction, or any unexpected incidence, and the severity thereof, associated with the clinical uses, studies, investigations, tests and marketing of a Licensed Product. For purposes of this Section 11.10, "unexpected" shall mean (i) for a non-marketed Licensed Product, an experience that is not identified in nature, severity or frequency in the current clinical investigator's confidential information brochure, and (ii) for a marketed Licensed Product, an experience which is not listed in the current labeling for such Licensed Product, and includes an event that may be symptomatically and patho-physiologically related to an event listed in the labeling but differs from the event because of increased frequency or greater severity or specificity. Each party further shall immediately notify the other of any information received regarding any threatened or pending action by a government agency which may affect the safety and efficacy claims of a Licensed Product. Upon receipt of any such information, the parties shall […***…]; provided, however, that nothing contained herein shall be construed as restricting either party's right to make a timely report of such matter to any government agency or take other action that it deems to be appropriate or required by applicable law or regulation.

11.11 Assignment. This Agreement shall not be assignable by any party without the prior written consent of the other (which consent shall not be unreasonably withheld, conditioned or delayed), except that Licensee may assign this Agreement to an Affiliate or to a successor in interest or transferee of all or substantially all of its assets.

11.12 Successors. Subject to the limitations on assignment herein, this Agreement shall be binding upon and inure to the benefit of the successors in interest and assigns of Licensors and Licensee. In order for such assignment to be effective any such successor or assignee of a party's interest shall expressly assume in writing the performance of all the terms and conditions of this Agreement to be performed by said party and such assignment shall not relieve the assignor of any of its obligations under this Agreement.

11.13 Expenses. Except as set forth in Section 3.4 hereof, Licensee and Licensors shall each bear its own expenses, including, without limitation, the fees and disbursements of its respective counsel and accountants, in connection with the negotiation and execution of this Agreement and the consummation of the transactions contemplated hereby.

11.14 Dispute Resolution. All disputes respecting this Agreement, including, inter alia, the termination of, or any other matter relating to or arising from, this Agreement, shall be resolved in binding arbitration in a proceeding administered by and in accordance with the rules and regulations of the American Arbitration Association. The action will take place in Delaware, unless the parties to the dispute agree otherwise. The judgment of the arbitrator shall be final, binding and conclusive and a judgment shall be entered pursuant to the Federal Arbitration Act in any federal court in the State of Delaware. The arbitrator shall not have authority to modify or change any of the terms of this Agreement. The parties and the arbitrator will treat the arbitration process and the activities which occur in the proceedings as confidential.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement, in duplicate originals, by their respective officers hereunto duly authorized, the day and year first above written.

MEDICIS PHARMACEUTICAL CORPORATION

By: /s/ Mark A. Prygocki, Sr.
Name: Mark A. Prygocki, Sr.
Title: Chief Financial Officer

BRUSILOW ENTERPRISES, INC.

By: /s/ Saul Brusilow, M.D.
Name:
Title:

/s/ Saul Brusilow, M.D.
SAUL W. BRUSILOW, M.D.

SCHEDULE A

PATENT RIGHTS

International Application Number:	PCT/US96/00940 (copy attached)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(71)(72) Applicant and Inventor: BRUSILOW, Saul, W. [US/US]; 4804 Keswick Road, Baltimore, MD 21201 (US).

(74) Agents: MURRAY, Robert, B. et al.; Nikaido, Marmelstein, Murray & Oram, Metropolitan Square, Suite 330 - G Street Lobby, 655 15th Street, NW, Washington, DC 20005-5701 (US).

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(54) Title: TRIGLYCERIDES AND ETHYL ESTERS OF PHENYLALKANOIC ACID AND PHENYLALKENOIC ACID USEFUL IN TREATMENT OF VARIOUS DISORDERS

(57) Abstract

Two new forms of prodrug for phenylacetate, of even congeners of phenylalkanoic acid and phenylalkenoic acids, which are the phenylalkanoic or phenylalkenoic esters of glycerol, or the ethyl esters of phenylalkanoic acid or phenylalkenoic acids. These forms of the drugs provide a convenient dosage form of the drugs. The prodrugs of the invention are useful to treat patients with diseases of nitrogen accumulation, patients with certain β-hemoglobinopathies, anemia, and cancer.

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TRIGLYCERIDES AND ETHYL ESTERS OF PHENYLALKANOIC ACID AND PHENYLALKENOIC ACID USEFUL IN TREATMENT OF VARIOUS DISORDERS

Background of the Invention

The present invention relates to compounds, pharmaceutical compositions, and methods for treating several conditions with prodrugs for phenylacetate as therapeutics agents.

Field of the Invention

Phenylalkanoic acids are known therapeutic agents for a variety of disorders. Phenylacetate is used for the treatment of nitrogen metabolism disorders, beta-hemoglobinopathies, anemia and cancer. Various phenylalkenoic acids can be used in the treatment of the same disorders. The prodrugs disclosed in the present invention arc useful therapeutic agents for a number of disorders, and possess some advantages over the forms of the drugs administered in the prior art.

Nitrogen Metabolism Disorders

In a healthy person, the potentially toxic nitrogenous compounds which accumulate as the body degrades proteins are synthesized into urea which is rapidly excreted into the urine. However, for those who suffer kidney failure, liver failure or inborn errors of urea synthesis, this pathway is defective. The accumulation of nitrogenous compounds resulting from such a blockage leads to considerable morbidity and mortality.

In the case of an inborn error of urea synthesis, the major metabolic abnormality is the inability of the body to convert waste nitrogen into urea. As a consequence, various nitrogenous metabolites accumulate in the body, the most toxic being ammonium,

although other materials, such as glutamine and alanine also increase.

Previous therapeutic approaches for treating patients with urea cycle enzymopathies (as well as other nitrogen accumulation diseases cited earlier) have been designed to reduce the requirement for urea synthesis by quantitative and qualitative manipulation of dietary protein, amino acids and/or their nitrogen free analogues. Generally speaking, however, the mortality of inborn errors of the urea-cycle remained high and success was measured in terms of increased survival time. Thus, for example, even with the above-cited therapeutic approaches, children with the neonatal form of these diseases rarely survive past one year of age (Maestri, et al., The Journal of Pediatrics , Vol. 119, No. 6, 923-928 (1991)).

Description of Related Art

A more recent approach to remedy this pervasive problem is described in U.S. Pat. No. 4,284,647 to Saul W. Brusilow, wherein benzoic acid, phenylacetic acid, or the salts thereof, convert the waste nitrogen into amino acid acylation products which the body can successfully excrete as urinary nitrogen. More specifically, the patent teaches that phenylacetate reacts with the nitrogen to form phenylacetylglutamine which is subsequently excreted by the body. Since such a reaction is in no way dependent on the urea synthesis or excretion, it is an effective treatment for those suffering from nitrogen accumulation diseases. See also “Treatment of Inborn Errors of Urea synthesis,” New England Journal of Medicine , 306; 1387-1392 (1982).

U.S. Pat. No. 4,457,942, also to Saul W. Brusilow, discloses that even-numbered phenylalkanoic acids can be advantageously used for the treatment of nitrogen accumulation diseases.

When administered to humans, even numbered phenylalkanoic acids, such as phenylbutyrate, can be

broken down by beta-oxidation, two carbon atoms at a time, to eventually yield phenylacetate which, as described above, has been found useful for removing waste nitrogen from the blood stream. The administration of even numbered phenylalkanoic acids such as phenylbutyrate has the advantage that the higher molecular weight compounds do not have the offensive odor which phenylbutyrate has.

The above treatments, although effective, have a substantial disadvantage. The dose of sodium phenylbutyrate for an adult with a urea cycle disorder is 20 grams/day. This requires that the patient take forty (40) tablets of 0.5 grams each, per day. Problems of patient compliance arise when such large daily doses are required. The administration of sodium phenylbutyrate has a second disadvantage to many patients – patients who should restrict their daily dose of sodium. The above daily dose of sodium phenylbutyrate provides 2.5 gm of sodium per day, every day (it is recommended that adults consume less than 2.4 grams/day total sodium).

The substitution in therapy of phenylacetate or phenylbutyrate, by the compounds of the present invention, provides the therapeutic compound in a more convenient dosage form. In addition, the compounds of the present invention may eliminate the peaks and valleys in drug levels since the breakdown of these higher molecular weight compounds by beta-oxidation is a gradual process. In addition, the Na component of the prior art is replaced with glycerol, which is a normal product of metabolism.

Cancer

Phenylbutyrate and phenylacetate are being investigated as a treatment for various malignant diseases. The exact mechanism by which this therapy causes improvement in the patient is not entirely clear.

It has been observed that primary central nervous system tumors are reminiscent of immature brain, and the immature brain is known to be more vulnerable to

damage by phenylacetate than the mature brain (as is observed in phenylketonuria). Sodium phenylacetate appears to promote the differentiation of cultured human glioblastoma cell lines with reduced expression of malignant phenotype.

Systemic treatment of rats bearing intracranial gliomas with phenylacetate resulted in significant tumor suppression with no apparent toxicity to the host. Early clinical results suggest that phenylacetate may become an important tool in the management of certain tumors in light of its demonstrated efficacy, and lack of toxicity (Samid et al., Cancer Research , 54, 891-895, 1994, and Cinatl et al., Cancer Letters , 70, 15-24, 1993).

A similar theory may be applied in treating prostate cancer with phenylacetate. The phenylacetate is thought to act as a differentiation inducer of leukemic and other less differentiated tumor cells, such as hormone refractory prostate cancer.

Cultured cells of androgen dependent prostate cell lines with sodium phenylacetate show inhibition of cell proliferation. In addition, such cells show reversion to non-malignant phenotype by in vivo and in vitro assessments (Samid et al., The Journal of Clinical Investigation , Vol. 19, 2288-2295, 1993).

Phenylacetate may exert an anti-tumor affect by another mechanism. Glutamine is the major nitrogen source for nucleic acid and protein synthesis, and substrate for energy in rapidly dividing normal and tumor cells. Compared to normal tissue, most tumors, due to decreased synthesis of glutamine along with accelerated utilization and catabolism, operate at limiting levels of glutamine availability and consequently are sensitive to further glutamine depletion. In the body, phenylacetate conjugates with glutamine, with subsequent renal excretion of phenylacetylglutamine. This pathway is the reason that phenylacetate administration is useful in the treatment of nitrogen accumulation diseases. Because phenylacetate removes glutamine, administration of phenylacetate may

limit the growth rate of rapidly dividing cells such as tumor cells.

By one or more of the above mechanisms, phenylacetate causes a decrease in tumor characteristics of a variety of tumor cells. Because of its known non-toxicity, phenylacetate is a promising therapeutic agent, either alone or in combination with other anti-tumor agents.

Hemoglobinopathies

Sodium phenylbutyrate is thought to cause improvement in certain ß-hemoglobinopathies because the sodium phenylbutyrate induces the expression of fetal hemoglobin. Thus the absent or aberrant ß-hemoglobin is substituted with fetal hemoglobin.

Numerous agents which induce the expression of fetal hemoglobin have been used to treat sickle cell anemia and ß-thalassemias. Some of the agents which increase the production of fetal hemoglobin however, have serious side effects that are not consistent with their use as long term therapeutic agents. However, sodium phenylacetate and sodium phenylbutyrate have been previously used to treat urea cycle disorders and are known to be very well tolerated and free of adverse reactions in clinical use. Preliminary clinical studies of patients with beta thalassemia indicate that treatment with sodium phenylbutyrate results in a response in many patients. The response is particularly good in patients with relatively high erythropoietin levels. Thus, combination therapy of the phenylbutyrate and erythropoietin may be effective. Hydroxyurea given orally has also been shown to increase hemoglobin levels in some thalassemia patients. Clinical studies of thalassemia patients treated with a combination of hydroxyurea and sodium phenylbutyrate has produced increased hemoglobin levels in some patients.

Summary of the Invention

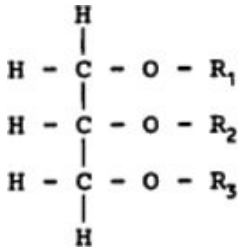
The compounds of the present invention, triglycerides of phenylalkanoic acids or phenylalkenoic acids, and ethyl esters of phenylalkanoic acids or phenylalkenoic acids, provide a more convenient dosage form of drugs for treatment of nitrogen accumulation disorders, cancer, anemia and hemoglobinopathies. The compounds of the invention are oils or soft fats. Where the prior art dose for an adult would have been forty 0.5 g tables/day, the present invention provides the same amount of active compound in approximately four (4) teaspoonfuls per day. The dosage form of the present invention also decreases sodium intake in patients, which is advantageous in certain patients, and may also provide the active component of the drug, the phenylalkanoic or phenylalkenoic acid, at a more constant level.

The compounds of the invention may be used for the treatment of nitrogen accumulation disorders, portal systemic encephalopathy, and diseases involving impaired hepatic function. Additionally, the use of triglycerides and/or the esters of the present invention alone or in combination with hydroxyurea and/or erythropoietin, may be used for the treatment of beta chain hemoglobinopathies. The compounds of the invention are suitable for the treatment for various leukemias and solid tumors.

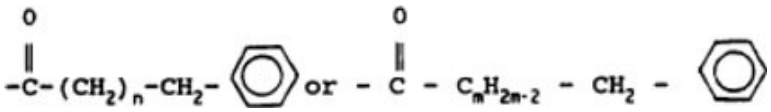
The compounds of the invention can be produced by standard esterification procedures. Additionally, many of the compounds of the invention are commercially available.

Description of the Preferred Embodiments

The present invention utilizes compounds of the formula:



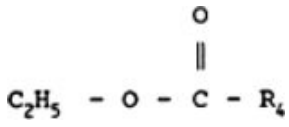
wherein R_1, R_2, and R_3 are independently, H,



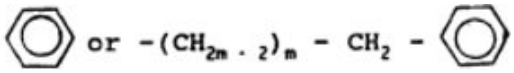
, and n is zero or an even number, m is an even number and at least one of R_1, R_2, and R_3, is not H.

The most preferred compounds are those wherein none of R_1, R_2 and R_3 is H. The advantage over the prior art of decreased dosage is greater with such triglycerides.

The present invention also utilizes ethyl esters of the formula II



(II)

wherein R_4 is  and n is zero or an even number, and m is an even number.

The compounds of the invention include compounds with substituents of even numbered congeners of phenylalkanoic and phenylalkenoic acids. Preferably the substituents contain 24 or fewer carbon atoms. Most preferably, n and m are 0, 2, 4 or 6.

The compounds of the present invention can be used separately or in the form of mixtures. The amount of the compounds of the present invention which is administered to patients for the present purposes can vary

widely from case to case. Normally, however, the daily dosage for the compounds should fall in the range of 450 to 600 mg/kg body weight for children, and from 9.9 to 13 grams for adults. The size and frequency of the dosages given at any time may be varied as described provided the indicated total daily does is not significantly modified. Preferably the compounds of the invention are administered orally, although in some circumstances, administration may be other routes such as topically or parenterally.

Metabolic Fates of the Compounds of the Invention

Pancreatic lipase is able to hydrolyse the triglyceride compounds of the invention to produce glycerol and phenylalkanoic acids or phenylalkenoic acids. The glycerol is then metabolized in the usual manner.

In their experiments with dogs, Raper and Wagner (Biochem Journal 22:188 (1928)) demonstrated that phenylalkanoic acids are oxidized at the beta carbon during metabolism to cause cleavage of two carbons at a time. Thus, they found that 80% of the phenylbutyrate administered to dogs appeared in the urine as the glycine conjugate of phenylacetate. Unlike dogs, man only produces an acetylation product of glutamine from phenylacetate. Thus, when phenylbutyrate is administered to a human as either a fatty acid or a salt thereof, the phenylacetate formed as a result of beta oxidation will acetylate the glutamine thus causing the formation of phenylacetylglutamine which will be excreted by the kidney. The beta oxidation process is not limited to phenylbutyrate. In fact, any even numbered phenylalkanoate can be metabolized to phenylacetate. Thus phenylhexanoate, phenyloctanoate and phenyldecanoate are also effective to control waste nitrogen levels.

Unsaturated fatty acids are oxidized by the same general pathway as saturated fatty acids. Two additional enzymes may be used, one which can reversibly shift the double bond from cis to trans configurations, and one

which hydrates the double bond to form hydroxy fatty acids. The compounds are then substrates for the beta oxidation enzymes.

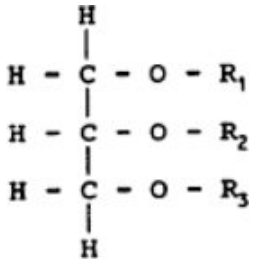
The ethyl esters of formula II are thought to be metabolized by spontaneous degradation in the intestine.

It is anticipated that the toxicity of tri-glycerides of phenylbutyrate and other compounds of this invention to patients would be low when these compounds are administered to patients because the fate of such compounds is phenylbutyrate which is beta oxidized to form phenylacetate. Glycerol is also produced, but it is a normal body constituent which is either converted to glucose or oxidized. For the ethyl esters, ethanol is produced, but in such small quantities as to be non-harmful. The phenylacetate metabolic product, on the other hand, has no known toxicity and is approved for investigational use in humans (IND #17123).

CLAIMS

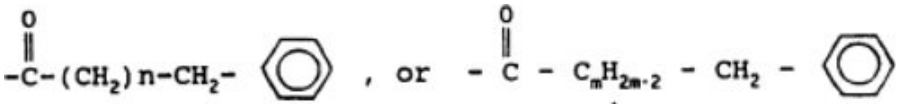
We claim:

1. A compound of the formula I



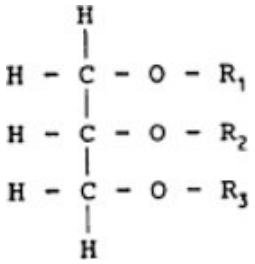
(I)

wherein R_1, R_2, and R_3 are independently, H,



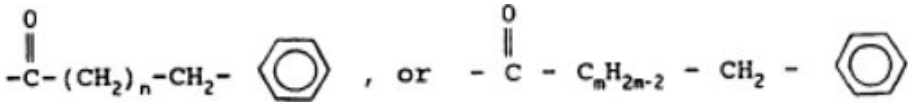
and n is zero or an even number, m is an even number and at least one of R_1, R_2, and R_3, is not H.

2. A pharmaceutical composition suitable for the treatment of nitrogen metabolism disorders, ß-hemoglobinopathies, anemia and cancer comprising a compound of the formula I



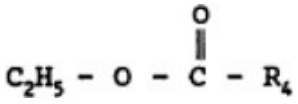
(I)

wherein R_1, R_2, and R_3 are independently, H,

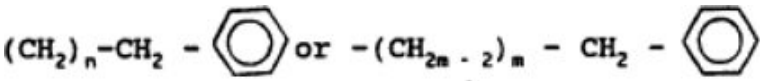


and n is zero or an even number, m is an even number and at least one of R_1, R_2, and R_3, is not H.

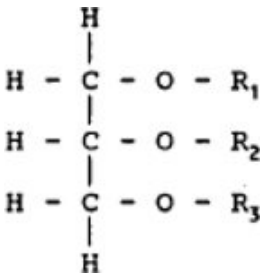
3. A pharmaceutical composition suitable for the treatment of nitrogen metabolism disorders, ß- hemoglobinopathies, anemia and cancer comprising ethyl esters of the formula II



(II)

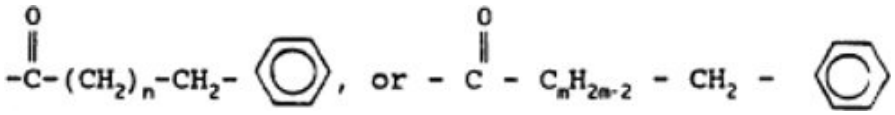
wherein R_4 is  , and n is zero or an even number, and m is an even number, together with at least one pharmaceutically acceptable excipient.

4. A method for the treatment of nitrogen metabolism disorders comprising administering to a patient in need of such treatment an effective amount of a compound of formula I

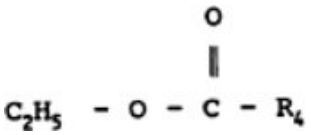


(I)

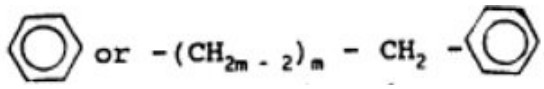
wherein R_1, R_2, and R_3 are independently, H,

 , and n is zero or an even number, m is an even number and at least one of R_1, R_2, and R_3 is not H.

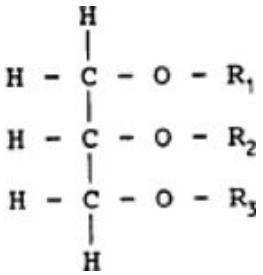
5. A method for the treatment of nitrogen accumulation diseases comprising administering to a patient in need of such treatment an effective amount of a compound of formula II



(II)

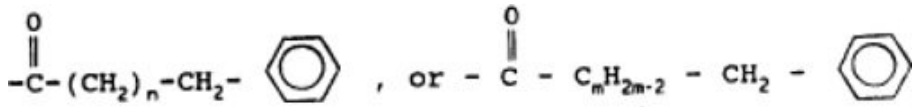
wherein R_4 is  , wherein n is zero or an even number and m is an even number.

6. A method for the treatment of tumors comprising administering to a patient in need of such treatment an anti-tumor effective amount of a compound of formula I

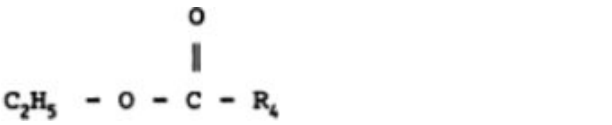


(I)

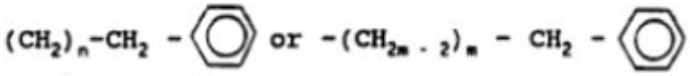
wherein R_1 , R_2 , and R_3 are independently, H,

 , and n is zero or an even number, m is an even number and at least one of R_1 , R_2 , and R_3 is not H.

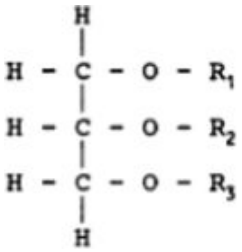
7. A method for the treatment of tumors comprising administering to a patient in need of such treatment an anti-tumor effective amount of a compound of formula II



(II)

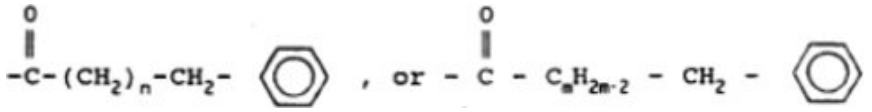
wherein R_4 is  wherein n is zero or an even number and m is an even number.

8. A method for the treatment of beta-hemoglobinopathies comprising administering to a patient in need of such treatment an effective amount of a compound of formula I



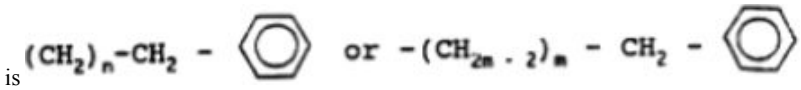
(I)

wherein R_1, R_2, and R_3 are independently, H,

 , and n is zero or an even number, m is an even number and at least one of R_1, R_2, and R_3 is not H.

9. A method for the treatment of beta-hemoglobinopathies comprising administering to a patient in need of such treatment an effective amount of a compound of formula II

(II)

wherein R_4 is  wherein n is zero or an even number and m is an even number.

10. The compound of claim 1 wherein none of R_1, R_2, and R_3 is H.

11. The composition of claim 2 wherein none of R_1, R_2, and R_3 is H.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00940

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07C 59/00, 57/30, 69/76
US CL :554/218, 220, 227; 560/8, 76
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 554/218, 220, 227; 560/8, 76

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 112, No. 25, 18 June 1990(Columbus, OH, USA), page 270, column 1, the abstract No. 231744t, WALSH, J.P. 'SN-1,2-Diacylglycerol kinase of Esherichia Coli. Diacylglycerol analogs define specificity and mechanism." Journal of Biological Chemistry. 1990, 265(8)(Eng).	1, 2, 10, 11
X,P	Chem. abstr. Vol. 123, No. 15, 09 October 1995(Columbus, OH, USA), page1315, column 1, the abstract No. 199405x, DEGRADO, W F. "Preparation of radiolabeled platelet GPIIb/IIIa receptor antagonist as imaging agents for the diagnosis of thromboembolic disorders." WO 94-22494.	4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 MAY 1996	Date of mailing of the international search report 13 JUN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DEBORAH D. CARR Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

SCHEDULE B

THIRD PARTY AGREEMENTS

The Johns Hopkins University Intellectual Property Policy (copy attached)

Intellectual Property Guidelines

THE JOHNS HOPKINS UNIVERSITY INTELLECTUAL PROPERTY POLICY

October 27, 1992

The Johns Hopkins University strives to support its faculty and employees in securing commercial development of intellectual and other property resulting from their research so that the benefits of that research may reach society at the earliest opportunity. This is consistent with the University's mission of developing new knowledge and facilitating the practical application of such knowledge to the benefit of the public. The University has developed policies and guidelines that provide incentives for its researchers while protecting the integrity of research emanating from this institution. Moreover, the University provides an array of administrative services to its Inventors to assist them in protecting rights to University Intellectual Property and fostering commercial development.

This document describes University policy relevant to Intellectual Property and lists the available University-wide resources. The policy shall be interpreted in a manner consistent with applicable federal and state statutes and implementing regulations. It shall apply to all students receiving remuneration for services, faculty, and staff of the University (with the exception of those covered under the Invention Policy of The Johns Hopkins University Applied Physics Laboratory). Faculty, staff and students shall be referred to as "faculty" throughout the remainder of this document. (For further definitions of terms, refer to Appendix II, Glossary.)

This revised Intellectual Property Policy supersedes that which was adopted by the Board of Trustees on October 13, 1988. It shall be effective on the date of its approval by the Board of Trustees. It shall apply to all new Inventions disclosed to the University after the effective date, as well as to those Inventions licensed after the policy's effective date regardless of date of disclosure. Inventions covered by the terms of a previous assignment remain subject to the policy under which they were negotiated. Inventors may elect in writing to receive royalties for those Inventions disclosed but not licensed prior to the date of Board approval as allowed under the previous University Invention Policy provided that such election was received by the appropriate Divisional office by the close of business on July 30, 1992. An Inventor choosing royalty distribution under the former policy shall be governed by all other provisions of the new policy

including the opportunity to benefit from ownership of equity. For any Invention licensed after the effective date of this policy, *regardless of choice of option* , University costs for patent prosecution, licensing, and license maintenance shall be reimbursed from Gross Revenues.

I. Intellectual Property: Definition

For purposes of this policy, Intellectual Property is defined as any new and useful process, machine, composition of matter, life form, article of manufacture, software, copyrighted work (see IV, E), or tangible property. It includes such things as new or improved devices, circuits, chemical compounds, drugs, genetically engineered biological organisms, data sets, software, musical processes, or unique and innovative uses of existing Inventions. Intellectual Property may or may not be patentable or copyrightable. It is created when something new and useful has been conceived or developed, or when unusual, unexpected, or non-obvious results, obtained with an existing Invention, can be practiced for some useful purpose. Intellectual Property can be created by one or more individuals each of whom, to be an Inventor, must have conceived of an essential element or have contributed substantially to its conceptual development.

II. University Responsibilities

The University acknowledges the importance of transferring its Intellectual Property in an appropriate and cost-effective manner. To that end, the University shall establish efficient mechanisms for technology transfer, so as to maximize the value of the technology to the faculty and the University.

A. The University Administration shall:

1. Provide oversight of Intellectual Property management and technology transfer to ensure adherence to University policies;

2. Assist the Divisions in establishing and maintaining effective technology transfer mechanisms and Divisional policies and procedures consistent with University policies;

3. Provide legal services and cooperate with the Divisions in promoting and licensing Intellectual Property; and

4. Take appropriate actions to protect the University's Intellectual Property.

B. Divisional Administrations shall:

1. Promote technology transfer in a manner consistent with the Division's objectives and academic environment;

2. Establish policies and procedures for technology transfer and the avoidance of conflicts of interests, consistent with University policies; and

3. Review and approve all agreements that convey or affect the University's rights to Intellectual Property originating in that Division.

III. Faculty Responsibilities

Faculty members who create Intellectual Property shall:

A. Disclose to appropriate University or Division officials the creation of Intellectual Property;

B. Conduct technology transfer activities in a manner consistent with University and Divisional policies and procedures, including those governing conflicts of commitment and conflicts of interest; and

C. Cooperate with the University in defending and prosecuting patents and in legal actions taken in response to infringement.

IV. Ownership of Intellectual Property

A. In general, the University has the right to obtain title to Intellectual Property developed as a result of support either directly from or channeled through the University.

B. University support is defined as financial or other support, regardless of origin, which is used in the discovery or development of Intellectual Property and is provided through University channels.

In the absence of University support, rights of ownership of Intellectual Property remain with the Inventor. Provision of an appointment shall not in and of itself be construed as University support for purposes of this definition.

C. The University may decline to accept any rights of ownership by assignment or otherwise, in which case all rights revert to the Inventor.

D. When software or other unpatented tangible research property (e.g., cell lines and data sets) is developed by faculty using University support, the University will own all rights to such property, including copyright (subject to agreements with appropriate funding sources).

E. Copyright to, and royalty from, literary or scholarly works in tangible or electronic form (e.g., textbooks and other curricular materials, reference works, journal articles, novels, music, photographs, etc.) produced by faculty members as a part of their usual teaching, service, and research activities, and which do not result directly as a specified deliverable from projects funded in whole or in part by the University or a sponsored research agency shall belong to the faculty who prepared such works and may be assigned or retained by them.

V. Revenue from Intellectual Property

A. General Principles

Revenues received as a result of Licensing Agreements in the form of cash royalties and/or equity holdings shall be distributed in such a manner as to encourage technology development within and technology transfer from the University. “Revenues” shall not include funds received for research support.

1. University costs for patent prosecution, licensing, and license maintenance, shall be reimbursed from Gross Revenues.

2. All shares of revenue, including the Inventor's, should contribute to the reimbursement of University costs for patent infringement actions. The manner and amount of such reimbursement will be determined by consultation between the Division Dean and the President so as to maintain fairness and adequate incentives in the distribution of revenue.

3. The schedule for distribution of Net Revenues shall be designed to provide personal incentives to Inventors.

4. The support and further development of technology transfer offices and functions shall be augmented fro5. m the distribution of Net Revenues to the Schools.

5. The portion of revenues distributed to the Inventors' laboratory(s) shall be limited to avoid imbalance within the Inventors' department(s).

6. Continued sensitivity to conflicts of interest require that certain types of research on a licensed Invention by its Inventor(s) and/or the University may be disallowed whatever the funding source. Sponsored research to advance the state of the art of existing Inventions is encouraged under those circumstances where the Inventor's participation presents little, if any, opportunity to compromise the integrity of the Inventor and the University. For review of cases involving potential Conflicts of Interest, the Division should create a faculty committee or committees to review and make recommendations to the Dean.

B. Net Royalty Revenue Distribution Schedule: see Appendix B

C. Equity Holdings

With careful safeguards, Licensing Agreements involving equity participation by the University and its faculty are permitted. Under appropriate circumstances, research sponsored by companies in which faculty and/or the University have equity holdings may also be permitted. Establishment and execution of specific rules and procedures for implementing the policy guidelines provided below are the responsibility of the Divisions.

1. University contracts with licensees must be negotiated by the appropriate University or Divisional office and not directly by the Inventor.

2. The Inventors' and the Institution's equity interest will not be traded until after a stipulated Trigger Date.

3. The Inventors' equity interest will be held in escrow for the benefit of the Inventor by the University.

4. Any association of the Inventor(s) with the licensee will be subject to disclosure, including compensation, prior approval, and annual reporting.

5. Divisions from which the Intellectual Property originates must have adequate policies and procedures for conflict of interest consistent with those outlined in section V.A.5.

D. Distribution of Equity Revenue

Inventors' Personal Share	Inventors' Laboratory(s) Share	Inventors' Department(s) Share	School Share	University Share
35%	15%	10%	30%	10%

Unlike royalty revenue, equity revenue distribution is sporadic and likely to occur only once. Cash received from the sale of shares allocated to the Inventors' Laboratory(s) Share will be apportioned in equal amounts annually to the appropriate laboratory(s) over the remaining life of the relevant U.S. Patent or the remaining years under the relevant License Agreement, whichever is shorter, unless the Dean of the School of the Inventor(s) and the Inventor(s) agree to another method of distribution.

E. Distribution After Termination or Death

1. The Inventors' personal share shall survive termination of affiliation with the University and, in the event of death of the Inventor, shall inure to his/her estate.

2. Upon termination of the Inventor's affiliation with the University, the Inventors' Laboratory Share, both the unspent portion and future allocations, will be reallocated to the Inventors' Department, School and University portions according to the applicable royalty distribution policy.

VI. Additional Provisions

A. Research

The University shall only enter into a research contract or other binding commitment to perform work that can reasonably be expected to be publishable, provide educational opportunities, and/or be in the public interest.

B. Use of the University's Name

All written or broadcast material containing the University's name for advertising, marketing, or other promotional purposes shall be submitted for approval to the Divisional Public Affairs Officer, and the Dean, *prior to* use of such material. A statement on the use of the University's name shall be included in all appropriate contracts between industry (company) and the University.

C. Publication

The University shall enter into contracts or other binding commitments to conduct research and training only if they permit the disclosure and publication of research. Delays in publication up to 120 days may be agreed to in order to permit time for filing of patent applications.

D. Confidentiality

The faculty shall not undertake research in which the sponsor:

1. prohibits the faculty member from disclosing the existence of the agreement; or

2. restricts the faculty member's public disclosure of information developed by that faculty member (see section C. above).

E. Avoidance of Conflict of Interest and Conflict of Commitment

1. Trust, good faith, and open discussion of controversial issues among colleagues have always been central to the life of the University. The activities of faculty members must be governed by thoughtful consideration of individual circumstances, rather than rigid rules. The requirement for reporting as outlined in the following paragraph is meant to ensure that conflicts of commitment and conflicts of interest will be considered openly and fairly, and that appropriate action will be taken to resolve those conflicts. Reporting thus serves to protect individual faculty members, The Johns Hopkins University, and academic freedom in general.

2. In cases where faculty enjoy rights to Intellectual Property under this policy, they have an obligation to report fully any outside activities and interests related to their teaching, research, or service to their Department Chair, Dean or other designated University official and **obtain their prior approval** before the activity begins. The report must be in writing and must include the names of companies for whom he/she consults, the number of days committed to each consulting agreement and a copy of any proposed consulting agreements associated with Intellectual Property. Consulting agreements must be reviewed for compliance with University policies and government regulations and approved by the appropriate Divisional office before the consultation can begin.

3. The holding of equity interest in a Commercial Venture by the University and faculty Inventor, and the receipt of royalties and acceptance of consultant fees, places a burden on the Inventor to report such financial interests in all relevant papers prepared for publication or oral presentation, in order to avoid later accusation that adverse results had been suppressed in order to enhance the marketability of the Invention.

F. Grievances

In the event an Inventor has a grievance about the University's handling of his/her Intellectual Property, he/she may appeal to the appropriate Divisional mechanism. An Investigator may take a grievance to the Office of the Provost if: his/her Division has no appeals mechanism or; he/she wishes to appeal a Divisional decision.

APPENDIX I

Limits on Inventors' Laboratory Share Of Net Revenues
See Appendix B

APPENDIX II

Glossary

Commercial Venture:
A Commercial Venture shall mean a start-up company, limited partnership, joint venture, or any other entity that has obtained a License to a Division's technology that involves equity. Ownership of a company's stock by the University in the endowment investment pool (EIP) will not alone define the company as a Commercial Venture.

Copyright :
Works of authorship in any tangible medium of expression can be copyrighted. Copyright does not protect mere ideas; it is the reproduction of the particular expression of the idea that receives protection by the federal statute known as the 1976 Copyright Act. A copyright gives an author or creator of an original expression (or in certain instances, the author's employer) the exclusive right to reproduce such expression; to distribute the expression (the right to control the first sale of an embodiment of a copyright); to display the original embodiment; and to prepare derivative works. To establish copyright it is necessary, prior to first Publication, to mark the work with the copyright symbol, ©, as well as the date and the name of the copyright owner.

Equity or Equity shares:
Equity or equity shares shall mean shares of common or preferred stock, warrants, options, convertible instruments, units of a limited partnership, or any other instrument conveying ownership interest in a Commercial Venture.

Gross Revenues :
Gross Revenues shall mean all income received by the University under a License Agreement. Excluded from Income shall be research funds (unless the research funds offset future royalty obligations) and maintenance fees received under the License agreement.

Income :
Income is the revenue paid as consideration for a **License** . Income includes one time payment or on-going revenues such as **License** fees, maintenance fees, minimum annual royalties, earned royalties, reimbursement of **Patent** expenses, and equity.

Intellectual Property :

Intellectual Property is any new and useful process, machine, composition of matter, life form, article of manufacture, software, **copyrighted** work, or **tangible property** . It includes such things as new or improved devices, circuits, chemical compounds, drugs, genetically engineered bacteria, data sets, software, musical processes, or unique and innovative uses of existing Inventions. Intellectual Property may or may not be patentable or copyrightable. Intellectual Property is created when something new and useful has been conceived or developed, or when unusual, unexpected, or non-obvious results have been obtained with an existing Invention which can be practiced for some useful purpose. Intellectual Property can be created by one or more individuals, each of whom to be an Inventor must have conceived of an essential element or have contributed substantially to its conceptual development.

Inventor :

An Inventor is one who makes a creative input to the conception of the Invention. U.S. **Patent** statutes require that only the true Inventor(s) be named on the Patent. *A coauthor or one who merely reduces the Invention to practice (i.e., successfully uses the Invention in its intended manner) is not an Inventor unless he makes a creative input to the conception.*

Inventors' Laboratory :

The Inventors' Laboratory is defined as the facilities which provide the opportunity for experimentation, observation and/or practice of the Inventors' particular field of study.

Invention :

A creation of Intellectual Property which did not exist previously.

License :

A License is a contract which awards to a party other than the owner(s) of the **Intellectual Property** the right to make, use, or sell the **Intellectual Property** . Licenses may be awarded on an exclusive or non-exclusive basis and may provide for payment of fees, royalties, or other income to the owner(s) of the **Intellectual Property** .

License Agreement :

A License Agreement shall mean an agreement conveying rights in a School's technology to the Commercial Venture, and under which equity is received as partial or full consideration.

Net Revenue :

Net Revenue shall mean Gross Revenue less unreimbursed Patent prosecution expenses, licensing expenses associated with a particular License Agreement.

Patent :

A U.S. Patent is a grant which gives the owner of the Invention covered by the Patent the right to exclude all others from making, using, or selling the Invention in the United States. In the United States, a Patent provides that exclusive right for 17 years. To qualify

for U.S. Patent protection, an Invention must be deemed new, useful, and non-obvious to one skilled in the art, and must not have been in public use or on sale in the United States or described in a printed **Publication** as defined below, anywhere in the world for more than one year prior to the filing date of the U.S. Patent application.

Patent rights in many foreign countries can be lost if there has been any disclosure of the Invention, verbal or written, anywhere in the world prior to filing the foreign Patent application. However, if the U.S. Patent application has been filed prior to any disclosure of the Invention, Patent applications may still be filed in foreign countries within one year of the U.S. filing date in those countries which adhere to an International Convention even if there has been an intervening **Publication** .

Publication :

As related to Inventions and Patents, a Publication is an enabling public disclosure of an Invention and may be verbal or printed. An enabling disclosure is one which will teach one skilled in the art how to practice the Invention. Printed Publications include abstracts and, in certain instances, grant proposals, funded or unfunded. A public disclosure is a non-privileged communication to one or more individuals from outside the University community. It is important to emphasize that the issuance of a Publication may jeopardize one's ability to secure a foreign Patent. Questions surrounding the implications of Publication can be addressed by the Patent Management Office or the appropriate technology transfer office.

Research Contract:

A Research Contract shall mean a separate agreement to conduct research related to licensed technology.

Tangible Property:

Tangible Property is anything having a physical embodiment (e.g., cell lines, software, devices, compositions of matter) whether or not **patent** able or **copyright** able.

Trigger Date:

Trigger Date shall mean the date the equity held by the University and by Divisional faculty Inventors is no longer subject to restrictions imposed by the University and may be traded, subject to any remaining restrictions imposed by law, the underwriters, or the Commercial Venture.

Next Section: **Intellectual Property Guidelines:** The Johns Hopkins University Revised Royalty Distribution for the School of Medicine

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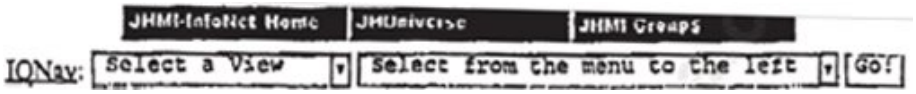
Intellectual Property Guidelines Navigation Page



Johns Hopkins School of Medicine: December, 1993
Technical Contact: www@infonet.welch.jhu.edu
JHMI-InfoNet: Aug 27, 1996

http://infonet.welch.jhu.edu/policy/intellectual_prop_guide/some_intpolA.html

SCHEDULE C

PROSECUTION OF PATENT RIGHTS

IN THE TERRITORY

Exhibit 31.3

Certification of Principal Executive Officer

I, Timothy P. Walbert, certify that:

1. I have reviewed this Amendment No. 2 to the quarterly report on Form 10-Q/A of Horizon Pharma plc; and

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report.

Date: May 26, 2017

/s/ Timothy P. Walbert
Timothy P. Walbert
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.4

Certification of Principal Financial Officer

I, Paul W. Hoelscher, certify that:

1. I have reviewed this Amendment No. 2 to the quarterly report on Form 10-Q/A of Horizon Pharma plc; and

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report.

Date: May 26, 2017

/s/ Paul W. Hoelscher
Paul W. Hoelscher
Executive Vice President, Chief Financial Officer
(Principal Financial Officer)