PUBLIC HEALTH SERVICE

PATENT LICENSE AGREEMENT - EXCLUSIVE and NON-EXCLUSIVE

COVER PAGE

For PHS internal use only:

License Number: L-116-2011/0

License Application Number: A-063-2009

Serial Number(s) of Licensed Patent(s) or Patent Application(s):

1. U.S. Patent 6,984,517, issued January 10, 2006, entitled "AAV5 Vector and Uses Thereof; U.S. Patent 7,479,554, issued January 20, 2009, entitled "AAV5 Nucleic Acids" as well as all issued and pending foreign counterparts [**HHS** Ref. No. E-127-1998/0];

2. U. S. Patent 6,855,314, issued February 15, 2005, entitled "AAV5 Vector for Transducing Brain Cells and Lung Cells" [HHS Ref. No. E-072-2000/0]

Licensee: Amsterdam Molecular Therapeutics (AMT) B.V.

Cooperative Research and Development Agreement (CRADA) Number (if a subject invention): N/A

Additional Remarks: This Patent License Agreement will replace PHS license L-119-2007/0 and any amendments thereto.

Public Benefit(s): Commercialization of this technology will benefit the public health by providing AAV5 based gene therapies to treat diseases originated from the brain and liver.

This Patent License Agreement, hereinafter referred to as the "Agreement", consists of this Cover Page, an attached Agreement, a Signature Page, Appendix A (List of Patent(s) or Patent Application(s)), Appendix B (Fields of Use and Territory), Appendix C (Royalties), Appendix D (Benchmarks and Performance), Appendix E (Commercial Development Plan), Appendix F (Example Royalty Report), and Appendix G (Royalty Payment Options). The Parties to this Agreement are:

- 1) The National Institutes of Health ("**NIH**") or the Food and Drug Administration ("**FDA**"), hereinafter singly or collectively referred to as "**PHS**", agencies of the United States Public Health Service within the Department of Health and Human Services ("**HHS**"); and
- The person, corporation, or institution identified above or on the Signature Page, having offices at the address indicated on the Signature Page, hereinafter referred to as "Licensee".

PHS PATENT LICENSE AGREEMENT - EXCLUSIVE and NON-EXCLUSIVE

PHS and Licensee agree as follows:

1. BACKGROUND

- 1.1 In the course of conducting biomedical and behavioral research, PHS investigators made inventions that may have commercial applicability.
- 1.2 By assignment of rights from **PHS** employees and other inventors, **HHS**, on behalf of the **Government**, owns intellectual property rights claimed in any United States or foreign patent applications or patents corresponding to the assigned inventions. **HHS** also owns any tangible embodiments of these inventions actually reduced to practice by **PHS**.
- 1.3 The Secretary of **HHS** has delegated to **PHS** the authority to enter into this **Agreement** for the licensing of rights to these inventions.
- 1.4 **PHS** desires to transfer these inventions to the private sector through commercialization licenses to facilitate the commercial development of products and processes for public use and benefit.
- 1.5 **Licensee** desires to acquire commercialization rights to certain of these inventions in order to develop processes, methods, or marketable products for public use and benefit.

2. DEFINITIONS

- 2.1 **"Affiliate(s)**" means a corporation or other business entity, which directly or indirectly is controlled by or controls, or is under common control with **Licensee**. For this purpose, the term "control" shall mean ownership of more than fifty percent (50%) of the voting stock or other ownership interest of the corporation or other business entity, or the power to elect or appoint more than fifty percent (50%) of the members of the governing body of the corporation or other business entity.
- 2.2 "Benchmarks" mean the performance milestones that are set forth in Appendix D.
- 2.3 "Commercial Development Plan" means the written commercialization plan attached as Appendix E.

- 2.4 **"Exempt Collaborator**" means a not-for-profit organization or academic institution that has entered into a formal collaboration and / or supply agreement with Licensee to conduct pre-clinical development and solely sponsor clinical trials of Licensed Product, excluding Supplied Materials, to treat an Ultra-Orphan Indication; in which Licensee may acquire clinical development and data for regulatory approval and sale of a Licensed Product.
- 2.5 "First Commercial Sale" means the initial transfer by or on behalf of Licensee or its sublicensees of Licensed Products or the initial practice of a Licensed Process by or on behalf of Licensee or its sublicensees in exchange for cash or some equivalent to which value can be assigned for the purpose of determining Net Sales.
- 2.6 "Government" means the Government of the United States of America.
- 2.7 "Licensed Fields of Use" means the fields of use a) and b) as identified in Appendix B.
- 2.8 "Licensed Patent Rights" shall mean:
 - Patent applications (including provisional patent applications and PCT patent applications) or patents listed in Appendix A, all divisions and continuations of these applications, all patents issuing from these applications, divisions, and continuations, and any reissues, reexaminations, and extensions of these patents;
 - (b) to the extent that the following contain one or more claims directed to the invention or inventions disclosed in 2.8(a):
 - (i) continuations-in-part of 2.8(a);
 - (ii) all divisions and continuations of these continuations-in-part;
 - (iii) all patents issuing from these continuations-in-part, divisions, and continuations;
 - (iv) priority patent application(s) of 2.8(a); and
 - (v) any reissues, reexaminations, and extensions of these patents;
 - (c) to the extent that the following contain one or more claims directed to the invention or inventions disclosed in 2.8(a): all counterpart foreign and U.S. patent applications and patents to 2.8(a) and 2.8(b), including those listed in Appendix A; and
 - (d) **Licensed Patent Rights** shall not include 2.8(b) or 2.8(c) to the extent that they contain one or more claims directed to new matter which is not the subject matter disclosed in 2.8(a).
- 2.9 "Licensed Processes" means processes which, in the course of being practiced, would be within the scope of one or more claims of the Licensed Patent Rights that have not been held unpatentable, invalid or unenforceable by an unappealed or unappealable judgment of a court of competent jurisdiction.
- 2.10 "Licensed Products" means tangible materials which, in the course of manufacture, use, sale, or importation, would be within the scope of one or more claims of the Licensed Patent Rights that have not been held unpatentable, invalid or unenforceable by an unappealed or unappealable judgment of a court of competent jurisdiction.
- 2.11 "Licensed Territory" means the geographical area identified in Appendix B.
- 2.12 "Marketing Approval" means any and all approvals (including price and reimbursement approvals, if required), licenses, registrations, or authorizations of regulatory authorities in any country that are necessary for the manufacture, use, storage, import, transport and/or sale of a Licensed Product in the Licensed Fields of Use in such country.
- 2.13 "Net Sales" means the total gross receipts for sales of Licensed Products or practice of Licensed Processes by or on behalf of Licensee or its sublicensees, and from leasing, renting, or otherwise making Licensed Products available to others without sale or other dispositions, whether invoiced or not, less returns and allowances, packing costs, insurance costs, freight out, taxes or excise duties imposed on the transaction (if separately invoiced), and wholesaler and cash discounts in amounts customary in the trade to the extent actually granted. No deductions shall be made for commissions paid to individuals, whether they are with independent sales agencies or regularly employed by Licensee, or sublicensees, and on its payroll, or for the cost of collections.
- 2.14 **"Orphan Indication**" means a disease that affects less than two hundred thousand (200,000) people in the United States as defined by the Food and Drug Administration or five (5) in ten thousand (10,000) people in the European Union as defined by the European Medicines Agency.
- 2.15 **"Practical Application**" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and in each case, under these conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or **Government** regulations available to the public on reasonable terms.
- 2.16 **"Research License"** means a nontransferable, nonexclusive license to make and to use **Licensed Products** or **Licensed Processes** as defined by the **Licensed Patent Rights** for purposes of research and not for purposes of commercial manufacture or distribution or in lieu of purchase.
- 2.17 **"Supplied Materials**" means (a) A helper plasmid for AAV5 5RepCap 5RepCapB containing the p5 promoter, the AAV5 Rep and AAV5 Cap genes and an SV40ori adjacent to the polyadenylation signal at the 3' end or equivalent; (b) A vector plasmid for AAV5,

pAAV5LacZ/pAAV5RnLacZ expressing nucleus localized beta-galactosidase contains the LacZ gene under control of Rous Sarcoma Virus (RSV) promoter between the AAV5 ITRs or equivalent both of which are described in Chiorini et at Virol;. 73(2):1309-19 (Feb. 1999), including any progeny, subclones, or unmodified derivatives thereof where "unmodified derivatives" is defined as set forth in the Uniform Biological Material Transfer Agreement as published in the Federal Register at 60(45): 12771-75 (March 8, 1995); and (c) Plasmid maps corresponding to items (a) and (b) as set forth in the Paragraph. Further, these **Supplied Materials** were supplied by **PHS** to **Licensee** under a Material Transfer Agreement.

- 2.18 **"Third Party Applicant**" shall mean any non-Licensee applicant from whom PHS receives a license application for Licensed Patent Rights in an indication for which proposed commercial development is not addressed in Licensee's then current Commercial Development Plan outlined in Appendix E of this Agreement.
- 2.19 "Ultra-Orphan Indication" means a disease that affects less than one (1) in Fifty Thousand (50,000) people in the United States or the European Union.

3. GRANT OF RIGHTS

- 3.1 **PHS** hereby grants and **Licensee** accepts, subject to the terms and conditions of this **Agreement**, an exclusive license and non-exclusive license, as specified in Appendix B, under the **Licensed Patent Rights** in the **Licensed Territory** to make and have made, to use and have used, to sell and have sold, to offer to sell, and to import any **Licensed Products** in the **Licensed Fields of Use** and to practice and have practiced any **Licensed Processes** in the **Licensed Fields of Use**.
- 3.2 This **Agreement** confers no license or rights by implication, estoppel, or otherwise under any patent applications or patents of **PHS** other than the **Licensed Patent Rights** regardless of whether these patents are dominant or subordinate to the **Licensed Patent Rights**.

4. SUBLICENSING

- 4.1 Upon written approval, which shall include prior review of any sublicense agreement by **PHS** and which shall not be unreasonably withheld, **Licensee** may enter into sublicensing agreements under the **Licensed Patent Rights**.
- 4.2 **Licensee** agrees that any sublicenses granted by it shall provide that the obligations to **PHS** of Paragraphs 5.1-5.4, 8.1, 10.1, 10.2, 12.5, and 13.8-13.10 of this **Agreement** shall be binding upon

the sublicensee as if it were a party to this **Agreement**. **Licensee** further agrees to attach copies of these Paragraphs to all sublicense agreements.

- 4.3 Any sublicenses granted by Licensee shall provide for the termination of the sublicense, or the conversion to a license directly between the sublicensees and PHS, at the option of the sublicensee, upon termination of this Agreement under Article 13. This conversion is subject to PHS approval (not to be unreasonably withheld) and contingent upon acceptance by the sublicensee of the remaining provisions of this Agreement.
- 4.4 **Licensee** agrees to forward to **PHS** a complete copy of each fully executed sublicense agreement postmarked within thirty (30) days of the execution of the agreement. To the extent permitted by law, **PHS** agrees to maintain each sublicense agreement in confidence.
- 5. STATUTORY AND PHS REQUIREMENTS AND RESERVED GOVERNMENT RIGHTS
 - 5.1 (a) **PHS** reserves on behalf of the **Government** an irrevocable, nonexclusive, nontransferable, royalty-free license for the practice of all inventions licensed under the **Licensed Patent Rights** throughout the world by or on behalf of the **Government** and on behalf of any foreign government or international organization pursuant to any existing or future treaty or agreement to which the **Government** is a signatory. Prior to the **First Commercial Sale**, **Licensee** agrees to provide **PHS** with reasonable quantities of **Licensed Products** or materials made through the **Licensed Processes** for **PHS** research use; and
 - (b) In the event that the Licensed Patent Rights are Subject Inventions made under a Cooperative Research and Development Agreement ("CRADA"), Licensee grants to the Government, pursuant to 15 U.S.C. §3710a(b)(l)(A), a nonexclusive, nontransferable, irrevocable, paid-up license to practice Licensed Patent Rights or have Licensed Patent Rights practiced throughout the world by or on behalf of the Government. In the exercise of this license, the Government shall not publicly disclose trade secrets or commercial or financial information that is privileged or confidential within the meaning of 5 U.S.C. §552(b)(4) or which would be considered as such if it had been obtained from a non-Federal party. Prior to the First Commercial Sale, Licensee agrees to provide PHS reasonable quantities of Licensed Products or materials made through the Licensed Processes for PHS research use.
 - 5.2 **Licensee** agrees that products used or sold in the United States embodying **Licensed Products** or produced through use of **Licensed Processes** shall be manufactured substantially in the United States, unless a written waiver is obtained in advance from **PHS**.
 - 5.3 Licensee acknowledges that PHS may enter into future CRADAs under the Federal Technology Transfer Act of 1986 that relate to the subject matter of this Agreement. Licensee agrees not to unreasonably deny requests for a Research License from future collaborators with PHS when acquiring these rights is necessary in order to make a CRADA project feasible. Licensee may request an opportunity to join as a party to the proposed CRADA.
 - 5.4 (a) In addition to the reserved license of Paragraph 5.1, PHS reserves the right to grant Research Licenses directly or to require Licensee to grant Research Licenses on reasonable terms. The purpose of these Research Licenses is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however, PHS shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of materials made through the Licensed Processes; and

- (b) In exceptional circumstances, and in the event that Licensed Patent Rights are Subject Inventions made under a CRADA, the Government, pursuant to 15 U.S.C. §3710a(b)(l)(B), retains the right to require the Licensee to grant to a responsible applicant a nonexclusive, partially exclusive, or exclusive sublicense to use the Licensed Patent Rights in the Licensed Field of Use on terms that are reasonable under the circumstances, or if Licensee fails to grant this license, the Government retains the right to grant the license itself. The exercise of these rights by the Government shall only be in exceptional circumstances and only if the Government determines:
 - (i) the action is necessary to meet health or safety needs that are not reasonably satisfied by Licensee;
 - (ii) the action is necessary to meet requirements for public use specified by Federal regulations, and these requirements are not reasonably satisfied by the **Licensee**; or
 - (iii) the Licensee has failed to comply with an agreement containing provisions described in 15 U.S.C. §3710a(c)(4)(B); and
- (c) The determination made by the **Government** under this Paragraph 5.4 is subject to administrative appeal and judicial review under 35 U.S.C. \$203(b).

6. ROYALTIES AND REIMBURSEMENT

- 6.1 **Licensee** agrees to pay **PHS** a noncreditable, nonrefundable license issue royalty as set forth in Appendix C.
- 6.2 Licensee agrees to pay PHS a nonrefundable minimum annual royalty as set forth in Appendix C.
- 6.3 Unless otherwise exempted in Paragraphs 6.13-6.19, Licensee agrees to pay PHS earned royalties as set forth in Appendix C.
- 6.4 Unless otherwise exempted in Paragraphs 6.13-6.19, Licensee agrees to pay PHS benchmark royalties as set forth in Appendix C.
- 6.5 Licensee agrees to pay PHS sublicensing royalties as set forth in Appendix C.
- 6.6 A patent or patent application licensed under this **Agreement** shall cease to fall within the **Licensed Patent Rights** for the purpose of computing earned royalty payments in any given country on the earliest of the dates that:
 - (a) the application has been abandoned and not continued;
 - (b) the patent expires or irrevocably lapses, or
 - (c) the patent has been held to be invalid or unenforceable by an unappealed or unappealable decision of a court of competent jurisdiction or administrative agency.
- 6.7 No multiple royalties shall be payable because any Licensed Products or Licensed Processes are covered by more than one of the Licensed Patent Rights. In the event that this Agreement and PHS license L-107-2007/0 as amended from time to time apply to the same product sold by the

Licensee or its sublicensees then the Licensee shall only pay earned royalties and benchmark royalties under this Agreement.

- 6.8 On sales of **Licensed Products** by **Licensee** to sublicensees or on sales made in other than an arms-length transaction, the value of the **Net Sales** attributed under this Article 6 to this transaction shall be that which would have been received in an arms-length transaction, based on sales of like quantity and quality products on or about the time of this transaction.
- 6.9 With regard to unreimbursed expenses associated with the preparation, filing, prosecution, and maintenance of all patent applications and patents included within the Licensed Patent Rights and paid by PHS prior to the effective date of this Agreement. Licensee shall pay PHS, as an additional royalty, on or before March 1, 2012, and upon PHS' submission of a statement and request for payment to Licensee, an amount equivalent to these unreimbursed expenses previously paid by PHS, the total amount should not exceed two hundred and fifty thousand U.S. dollars (\$250,000). If this Agreement is terminated by Licensee on or before March 1, 2012, Licensee agrees to pay the amount in full within sixty (60) days before termination.
- 6.10 With regard to unreimbursed expenses associated with the preparation, filing, prosecution, and maintenance of all patent applications and patents included within the Licensed Patent Rights and paid by PHS on or after the effective date of this Agreement. PHS, at its sole option, may require Licensee:
 - (a) to pay **PHS** on an annual basis, within sixty (60) days of **PHS**' submission of a statement and request for payment, a royalty amount equivalent to these unreimbursed expenses paid during the previous calendar year;
 - (b) to pay these unreimbursed expenses directly to the law firm employed by **PHS** to handle these functions. However, in this event, **PHS** and not **Licensee** shall be the client of the law firm; or
 - (c) in limited circumstances, Licensee may be given the right to assume responsibility for the preparation, filing, prosecution, or maintenance of any patent application or patent included with the Licensed Patent Rights. In that event, Licensee shall directly pay the attorneys or agents engaged to prepare, file, prosecute, or maintain these patent applications or patents and shall provide PHS with copies of each invoice associated with these services as well as documentation that these invoices have been paid.
- 6.11 **PHS** agrees, upon written request, to provide **Licensee** with summaries of patent prosecution invoices for which **PHS** has requested payment from the **Licensee** under Paragraphs 6.9 and 6.10. **Licensee** agrees that all information provided by **PHS** related to patent prosecution costs

shall be treated as confidential commercial information and shall not be released to a third party except as required by law or a court of competent jurisdiction.

- 6.12 **Licensee** may elect to surrender its rights in any country of the **Licensed Territory** under any of the **Licensed Patent Rights** upon sixty (60) days written notice to **PHS** and owe no payment obligation under Paragraph 6.10 for patent-related expenses paid in that country after ninety (90) days of the effective date of the written notice.
- 6.13 Exemption for Ultra-Orphan Indication Research
 - (a) **Licensee** shall be permitted, upon **PHS** consent, (not to be unreasonably withheld), to manufacture and supply **Licensed Product**, excluding **Supplied Materials**, to an **Exempt Collaborator** for use solely in pre-clinical and clinical development to treat an

Ultra-Orphan Indication. Prior to commencement of manufacturing of Licensed Product for an Exempt Collaborator, Licensee shall request permission in writing and must obtain written consent from PHS. Additional documentation to establish an Exempt Collaborator may be required by PHS.

- (b) For avoidance of doubt, Licensee shall retain Supplied Materials and shall not release Supplied Materials alone to an Exempt Collaborator.
- (c) Upon receipt of written consent from **PHS** for manufacturing of a **Licensed Product** for an **Exempt Collaborator**. **Licensee** shall not be obligated to pay **Benchmark** royalties which would have been payable under **Appendix C**, Section IV for **Benchmarks** triggered by clinical trials solely sponsored by the **Exempt Collaborator** until such time as **Licensee** exercises its option to acquire the clinical development from the **Exempt Collaborator**.
- (d) Upon acquisition of the clinical development from an Exempt Collaborator. Licensee shall pay PHS royalties which become payable from that point onwards in accordance with Appendix C, Section IV. Licensee must inform PHS in writing within thirty (30) days of Licensee's decision to acquire or not acquire clinical development from the Exempt Collaborator.
- (e) For avoidance of doubt, **PHS** shall consider **Licensee**'s sponsorship or co-sponsorship of a clinical trial or regulatory submission for a **Licensed Product** to treat an **Ultra-Orphan Indication** as an acquisition of clinical development from an **Exempt Collaborator**.
- (f) Earned royalty payments on **Net Sales** specified in **Appendix C**, Section III shall not be applicable to **Licensed Product** manufactured for research and clinical trials conducted by an **Exempt Collaborator** approved by **PHS** per Paragraph 6.13.
- (g) In lieu of earned royalty payments, Licensee shall pay PHS a royalty payment of ten thousand U.S. dollars (\$10,000) for each collaboration approved by PHS with an Exempt Collaborator. Such royalty shall be due within thirty (30) days of the date of PHS written consent per Paragraph 6.13. In the event that several licenses granted by PHS to the Licensee apply to the same product, only a single payment of \$10,000 will be payable per collaboration.
- 7. PATENT FILING, PROSECUTION, AND MAINTENANCE
 - 7.1 Except as otherwise provided in this Article 7, **PHS** agrees to take responsibility for, but to consult with, the **Licensee** in the preparation, filing, prosecution, and maintenance of any and all patent applications or patents included in the **Licensed Patent Rights** and shall furnish copies of relevant patent-related documents to **Licensee**.
 - 7.2 Upon **PHS**' written request, **Licensee** shall assume the responsibility for the preparation, filing, prosecution, and maintenance of any and all patent applications or patents included in the **Licensed Patent Rights** and shall, on an ongoing basis, promptly furnish copies of all patent-related documents to **PHS**. In this event, **Licensee** shall, subject to the prior approval of **PHS**, select registered patent attorneys or patent agents to provide these services on behalf of **Licensee** and **PHS**. **PHS** shall provide appropriate powers of attorney and other documents necessary to undertake this action to the patent attorneys or patent agents providing these services. **Licensee** and its attorneys or agents shall consult with **PHS** in all material aspects of the preparation, filing, prosecution and maintenance of patent applications and patents included within the **Licensed**

Patent Rights and shall provide PHS sufficient opportunity to comment on any document that Licensee intends to file or to cause to be filed with the relevant intellectual property or patent office.

- 7.3 At any time, **PHS** may provide **Licensee** with written notice that **PHS** wishes to assume control of the preparation, filing, prosecution, and maintenance of any and all patent applications or patents included in the **Licensed Patent Rights** such that the terms of Paragraph 7.1 shall then apply. If **PHS** elects to reassume these responsibilities, **Licensee** agrees to cooperate fully with **PHS**, its attorneys, and agents in the preparation, filing, prosecution, and maintenance of any and all patent applications or patents included in the **Licensed Patent Rights** and to provide **PHS** with complete copies of any and all documents or other materials that **PHS** deems necessary to undertake such responsibilities. **Licensee** shall be responsible for all costs associated with transferring patent prosecution responsibilities to an attorney or agent of **PHS**' choice.
- 7.4 Each party shall promptly inform the other as to all matters that come to its attention that may materially affect the preparation, filing, prosecution, or maintenance of the **Licensed Patent Rights** and permit each other to provide comments and suggestions with respect to the preparation, filing, prosecution, and maintenance of **Licensed Patent Rights**, which comments and suggestions shall be considered by the other party.
- 8. RECORD KEEPING

8.1 Licensee agrees to keep accurate and correct records of Licensed Products made, used, sold, or imported and Licensed Processes practiced under this Agreement appropriate to determine the amount of royalties due PHS. These records shall be retained for at least five (5) years following a given reporting period and shall be available during normal business hours for inspection, at the expense of PHS, by an accountant selected by PHS for the sole purpose of verifying reports and royalty payments hereunder. The accountant shall only disclose to PHS information relating to the accuracy of reports and royalty payments made under this Agreement. Such inspections may be made no more than once each calendar year, with reasonable efforts to minimize disruption of Licensee's normal business activities. Such records for any particular calendar quarter shall be subject to no more than one (1) inspection. If an inspection shows an underreporting or underpayment in excess of five percent (5%) for any twelve (12) month period, then Licensee shall reimburse PHS for the cost of the inspection at the time Licensee pays the unreported royalties, including any additional royalties as required by Paragraph 9.8. All royalty payments required under this Paragraph shall be due within sixty (60) days of the date PHS provides Licensee notice of the payment due.

9. REPORTS ON PROGRESS, BENCHMARKS, SALES, AND PAYMENTS

- 9.1 Prior to signing this Agreement, Licensee has provided PHS with the Commercial Development Plan in Appendix E, under which Licensee intends to bring the subject matter of the Licensed Patent Rights to the point of Practical Application. This Commercial Development Plan is hereby incorporated by reference into this Agreement. Based on this plan, performance Benchmarks are determined as specified in Appendix D.
- 9.2 Licensee shall provide written annual reports on its product development progress or efforts to commercialize under the Commercial Development Plan for each of the Licensed Fields of Use within sixty (60) days after December 31 of each calendar year. These progress reports shall include, but not be limited to: progress on research and development, status of applications for regulatory approvals, manufacturing, sublicensing, marketing, importing, and sales during the preceding calendar year, as well as, plans for the present calendar year. PHS also encourages these reports to include information on any of Licensee's public service activities that relate to the Licensed Patent Rights. If reported progress differs from that projected in the Commercial

Development Plan and **Benchmarks**, **Licensee** shall explain the reasons for these differences. In the annual report, **Licensee** may propose amendments to the **Commercial Development Plan**, acceptance of which by **PHS** may not be denied unreasonably. **Licensee** agrees to provide any additional information reasonably required by **PHS** to evaluate **Licensee**'s performance under this **Agreement**. **Licensee** may amend the Benchmarks at any time upon written approval by **PHS**. **PHS** shall not unreasonably withhold approval of any request of **Licensee** to extend the time periods of this schedule if the request is supported by a reasonable showing by **Licensee** of diligence in its performance under the **Commercial Development Plan** and toward bringing the **Licensed Products** to the point of **Practical Application** as defined in 37 C.F.R. §404.3(d). **Licensee** shall amend the **Commercial Development Plan** and **Benchmarks** at the request of **PHS** to address any **Licensed Fields of Use** not specifically addressed in the plan originally submitted.

- 9.3 Licensee shall report to PHS the dates for achieving Benchmarks specified in Appendix D and the First Commercial Sale in each country in the Licensed Territory within thirty (30) days of such occurrences.
- 9.4 Licensee shall submit to PHS, within sixty (60) days after each calendar half-year ending June 30 and December 31, a royalty report, as described in the example in Appendix F, setting forth for the preceding half-year period the amount of the Licensed Products sold or Licensed Processes practiced by or on behalf of Licensee in each country within the Licensed Territory, the Net Sales, and the amount of royalty accordingly due. With each royalty report, Licensee shall submit payment of earned royalties due. If no earned royalties are due to PHS for any reporting 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 detailed listing of all deductions made under Paragraph 2.13 to determine Net Sales made under Article 6 to determine royalties due.
- 9.5 **Licensee** agrees to forward semi-annually to **PHS** a copy of these reports received by **Licensee** from its sublicensees during the preceding half-year period as shall be pertinent to a royalty accounting to **PHS** by **Licensee** for activities under the sublicense.
- 9.6 Royalties due under Article 6 shall be paid in U.S. dollars and payment options are listed in Appendix G. For conversion of foreign currency to U.S. dollars, the conversion rate shall be the New York foreign exchange rate quoted in *The Wall Street Journal* on the day that the payment is due. Any loss of exchange, value, taxes, or other expenses incurred in the transfer or conversion to U.S. dollars shall be paid entirely by Licensee. The royalty report required by Paragraph 9.4 shall be mailed to PHS at its address for Agreement Notices indicated on the Signature Page.
- 9.7 **Licensee** shall be solely responsible for determining if any tax on royalty income is owed outside the United States and shall pay the tax and be responsible for all filings with appropriate agencies of foreign governments.
- 9.8 Additional royalties may be assessed by **PHS** on any payment that is more than ninety (90) days overdue at the rate of one percent (1%) per month. This one percent (1%) per month rate may be applied retroactively from the original due date until the date of receipt by **PHS** of the overdue payment and additional royalties. The payment of any additional royalties shall not prevent **PHS** from exercising any other rights it may have as a consequence of the lateness of any payment.
- 9.9 All plans and reports required by this Article 9 and marked "confidential" by **Licensee** shall, to the extent permitted by law, be treated by **PHS** as commercial and financial information obtained from a person and as privileged and confidential, and any proposed disclosure of these records by the **PHS** under the Freedom of Information Act (FOIA), 5 U.S.C. §552 shall be subject to the predisclosure notification requirements of 45 C.F.R. §5.65(d).
- 9.10 In the event PHS receives a license application from a Third Party Applicant for commercial development of one or more Licensed Products or Licensed Processes in the exclusive Licensed Fields of Use, as they pertain to Licensed Patent Rights for which the proposed commercial development is not specifically addressed in Licensee's then-current Commercial Development Plan ("Third Party Applications"), PHS shall notify Licensee, in writing, of the existence of the Third Party Applicant's license application. Upon receipt of the written notice, Licensee shall respond in writing by either: (a) amending its Commercial Development Plan within one hundred and

twenty (120) days in a manner acceptable to PHS to include a clinical research and development program for the proposed commercial development of the Third Party Applications including revised Benchmarks to be incorporated into Appendix E, and acceptance of the amendment to the Commercial Development Plan by PHS shall take into account if Licensee has already carried out work in respect of such Third Party Applications prior to notification by PHS; or (b) amending its Commercial Development Plan within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applicant) in a manner acceptable to PHS to include a joint pre-clinical research and development program with the Third Party Applicant for the proposed commercial development of the Third Party Applications; or (c) granting an exclusive or non-exclusive sublicense under commercially reasonable terms to the Third Party Applicant under Licensed Patent Rights in respect of the Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applications within one-hundred eighty (180) days (or such longer period agreed by Licensee and such Third Party Applicant); or both (b) and (c). If Licensee does not respond to the written notice as described in this Paragraph 9.10, and after thirty (30) days of final notice being sent to Licensee, PHS may remove the Licensed Products or Licensee I Processes in respect of the Third Party Applications from the exclusive Licensed Field of Use in this Agreement, and PHS shall be free to

10. PERFORMANCE

- 10.1 Licensee shall use its reasonable commercial efforts to bring the Licensed Products and Licensed Processes to Practical Application. "Reasonable commercial efforts" for the purposes of this provision shall include adherence to the Commercial Development Plan in Appendix E and performance of the Benchmarks in Appendix D. The efforts of a sublicensee shall be considered the efforts of Licensee.
- 10.2 Upon the **First Commercial Sale**, until the expiration or termination of this **Agreement**, **Licensee** shall use its reasonable commercial efforts to make **Licensed Products** and **Licensed Processes** reasonably accessible to the United States public.
- 10.3 Licensee agrees, after its First Commercial Sale, to make reasonable quantities of Licensed Products or materials produced through the use of Licensed Processes available to patient assistance programs at cost. Patient assistance programs are programs run by pharmaceutical companies to provide free medications to people who cannot afford to buy their medicine. For each indication in each calendar year, the quantity of Licensed Products to be made available under this provision available to patient assistance programs at cost shall be defined as the higher of: (i) the maximum quantity of Licensed Products for such indication that was available in the previous calendar year (whether or not such Licensed Products were actually supplied); and (ii) five (5) percent of the total number of Licensed Products for such indication prescribed within the United States and its dependant territories in the previous calendar year.
- 10.4 **Licensee** agrees, after its **First Commercial Sale** in a country in the **Licensed Territory** and as part of its marketing and product promotion in such country, to develop educational materials (e.g., brochures, website, etc.) directed to patients and physicians in that country detailing the **Licensed**

Products or medical aspects of the prophylactic and therapeutic uses of the Licensed Products to the extent permitted by law in such country.

10.5 Licensee agrees to supply, upon request, to the Mailing Address for Agreement Notices indicated on the Signature Page, the Office of Technology Transfer, NIH with inert samples of the Licensed Products or Licensed Processes or their packaging for educational and display purposes only

11. INFRINGEMENT AND PATENT ENFORCEMENT

- 11.1 **PHS** and **Licensee** agree to notify each other promptly of each infringement or possible infringement of the **Licensed Patent Rights**, as well as, any facts which may materially affect the validity, scope, or enforceability of the **Licensed Patent Rights** of which either party becomes aware.
- 11.2 Pursuant to this Agreement and the provisions of 35 U.S.C. Part 29. Licensee may in accordance with the provisions of Paragraph 11.3:
 - (a) bring suit in its own name, at its own expense, and on its own behalf for infringement of presumably valid claims in the Licensed Patent Rights;
 - (b) in any suit, enjoin infringement and collect for its use, damages, profits, and awards of whatever nature recoverable for the infringement; or
 - (c) settle any claim or suit for infringement of the Licensed Patent Rights .provided, however, that PHS and appropriate Government authorities shall have the first right to take such actions.
- 11.3 If Licensee desires to initiate a suit for patent infringement, Licensee shall notify PHS in writing. If PHS does not notify Licensee of its intent to pursue legal action within ninety (90) days, Licensee shall be free to initiate suit. PHS shall have a continuing right to intervene in the suit. Licensee shall take no action to compel the Government either to initiate or to join in any suit for patent infringement. Licensee may request the Government to initiate or join in any suit if necessary to avoid dismissal of the suit Should the Government be made a party to any suit by motion or any other action of Licensee, Licensee shall reimburse the Government for any costs, expenses, or fees which the Government incurs as a result of the motion or other action. In all cases, Licensee agrees to keep PHS reasonably apprised of the status and progress of any litigation. Before Licensee commences an infringement action, Licensee shall notify PHS and give careful consideration to the views of PHS and to any potential effects of the litigation on the public health in deciding whether to bring suit.
- 11.4 In the event that a declaratory judgment action alleging invalidity or non-infringement of any of the Licensed Patent Rights shall be brought against Licensee or raised by way of counterclaim or affirmative defense in an infringement suit brought by Licensee under Paragraph 11.3, pursuant to this Agreement and the provisions of 35 U.S.C. Part 29 or other statutes, Licensee may:
 - (a) defend the suit in its own name, at its own expense, and on its own behalf for presumably valid claims in the Licensed Patent Rights;

- (b) in any suit, ultimately to enjoin infringement and to collect for its use, damages, profits, and awards of whatever nature recoverable for the infringement; and
- (c) settle any claim or suit for declaratory judgment involving the Licensed Patent Rights-provided, however, that PHS and appropriate Government authorities shall have the first right to take these actions and shall have a continuing right to intervene in the suit; and
- (d) If PHS does not notify Licensee of its intent to respond to the legal action within a reasonable time, Licensee shall be free to do so. Licensee shall take no action to compel the Government either to initiate or to join in any declaratory judgment action. Licensee may request the Government to initiate or to join any suit if necessary to avoid dismissal of the suit. Should the Government be made a party to any suit by motion or any other action of Licensee, Licensee shall reimburse the Government for any costs, expenses, or fees, which the Government incurs as a result of the motion or other action. If Licensee elects not to defend against the declaratory judgment action, PHS, at its option, may do so at its own expense. In all cases, Licensee agrees to keep PHS reasonably apprised of the status and progress of any litigation. Before Licensee commences an infringement action, Licensee shall notify PHS and give careful consideration to the views of PHS and to any potential effects of the litigation on the public health in deciding whether to bring suit.
- 11.5 In any action under Paragraphs 11.2, 11.3 or 11.4 the expenses including costs, fees, attorney fees, and disbursements, shall be paid by Licensee. The value of any recovery made by Licensee through court judgment or settlement shall be treated as Net Sales and subject to earned royalties.
- 11.6 **PHS** shall cooperate fully with **Licensee** in connection with any action under Paragraphs 11.2, 11.3 or 11.4. **PHS** agrees promptly to provide access to all necessary documents and to render reasonable assistance in response to a request by **Licensee**.
- 12. NEGATION OF WARRANTIES AND INDEMNIFICATION
 - 12.1 **PHS** offers no warranties other than those specified in Article 1.
 - 12.2 PHS does not warrant the validity of the Licensed Patent Rights and makes no representations whatsoever with regard to the scope of the Licensed Patent Rights, or that the Licensed Patent Rights may be exploited without infringing other patents or other intellectual property rights of third parties.
 - 12.3 **PHS** MAKES NO WARRANTIES, EXPRESS OR IMPLIED, OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OF ANY SUBJECT MATTER DEFINED BY THE CLAIMS OF THE **LICENSED PATENT RIGHTS** OR TANGIBLE MATERIALS RELATED THERETO.
 - 12.4 PHS does not represent that it shall commence legal actions against third parties infringing the Licensed Patent Rights.
 - 12.5 Licensee shall indemnify and hold PHS, its employees, students, fellows, agents, and consultants harmless from and against all liability, demands, damages, expenses, and losses, including but not limited to death, personal injury, illness, or property damage in connection with or arising out of:
 - (a) the use by or on behalf of Licensee, its sublicensees, directors, employees, or third parties of any Licensed Patent Rights; or
 - (b) the design, manufacture, distribution, or use of any Licensed Products, Licensed Processes or materials by Licensee, or other products or processes developed in connection with or arising out of the Licensed Patent Rights.
 - 12.6 Licensee agrees to maintain a liability insurance program consistent with sound business practice.

13. TERM, TERMINATION, AND MODIFICATION OF RIGHTS

- 13.1 This **Agreement** is effective when signed by all parties, unless the provisions of Paragraph 14.16 are not fulfilled, and shall extend to the expiration of the last to expire of the **Licensed Patent Rights** unless sooner terminated as provided in this Article 13.
- 13.2 In the event that **Licensee** is in default in the performance of any material obligations under this **Agreement**, including but not limited to the obligations listed in Paragraph 13.5, and if the default has not been remedied within ninety (90) days after the date of notice in writing of the default, **PHS** may terminate this **Agreement** by written notice and pursue outstanding royalties owed through procedures provided by the Federal Debt Collection Act.
- 13.3 In the event that **Licensee** becomes insolvent, files a petition in bankruptcy, has such a petition filed against it that is not discharged within ninety (90) days, determines to file a petition in bankruptcy, **Licensee** shall immediately notify **PHS** in writing. Furthermore, **PHS** shall have the right to terminate this **Agreement** immediately upon **Licensee**'s receipt of written notice.
- 13.4 **Licensee** shall have a unilateral right to terminate this **Agreement** or any licenses in any country or territory by giving **PHS** sixty (60) days written notice to that effect.
- 13.5 **PHS** shall specifically have the right to terminate or modify, at its option, this **Agreement**, if **PHS** determines that the **Licensee**:
 - (a) is not executing the Commercial Development Plan submitted with its request for a license and the Licensee cannot otherwise demonstrate to PHS' satisfaction that the Licensee has taken, or can be expected to take within a reasonable time, effective steps to achieve Practical Application of the Licensed Products or Licensed Processes;

- (b) has not achieved the **Benchmarks** as may be modified under Paragraph 9.2;
- (c) has willfully made a false statement of, or willfully omitted a material fact in the license application or in any report required by this **Agreement**;
- (d) has committed a material breach of a covenant or agreement contained in this Agreement;
- (e) is not keeping Licensed Products in a commercially reasonable manner available to the public after commercial use commences;
- (f) cannot reasonably satisfy unmet health and safety needs; or
- (g) cannot reasonably justify a failure to comply with the domestic production requirement of Paragraph 5.2 unless waived.
- 13.6 In making the determination referenced in Paragraph 13.5, PHS shall take into account (a) the normal course of such commercial development programs relating to gene therapy conducted with sound and reasonable business practices and judgment, (b) regulatory considerations, and the annual reports submitted by Licensee under Paragraph 9.2. Prior to invoking termination or modification of this Agreement under Paragraph 13.5, PHS shall give written notice to Licensee providing Licensee specific notice of, and a ninety (90) day opportunity to respond to, PHS' concerns as to the items referenced in 13.5(a)-13.5(g). If Licensee fails to alleviate PHS' concerns as to the items

referenced in 13.5(a)-13.5(g) or fails to initiate corrective action to PHS' reasonable satisfaction, PHS may terminate this Agreement.

- 13.7 When the public health and safety so require, and after written notice to Licensee providing Licensee a sixty (60) day opportunity to respond, PHS shall have the right to require Licensee to grant sublicenses to responsible applicants, on reasonable terms, in any Licensed Fields of Use under the Licensed Patent Rights, unless Licensee can reasonably demonstrate that the granting of the sublicense would not materially increase the availability to the public of the subject matter of the Licensed Patent Rights. PHS shall not require the granting of a sublicense unless the responsible applicant has first negotiated in good faith with Licensee.
- 13.8 **PHS** reserves the right according to 35 U.S.C. 5209(d)(3) to terminate or modify this **Agreement** if it is determined that this action is necessary to meet the requirements for public use specified by federal regulations issued after the date of the license and these requirements are not reasonably satisfied by **Licensee**.
- 13.9 Within thirty (30) days of receipt of written notice of PHS' unilateral decision to modify or terminate this Agreement, Licensee may, consistent with the provisions of 37 C.F.R. §404.11, appeal the decision by written submission to the designated PHS official. The decision of the designated PHS official shall be the final agency decision. Licensee may thereafter exercise any and all administrative or judicial remedies that may be available.
- 13.10 Within ninety (90) days of expiration or termination of this Agreement under this Article 13, a final report shall be submitted by Licensee. Any royalty payments, including those incurred but not yet paid (such as the full minimum annual royalty), and those related to patent expense, due to PHS shall become immediately due and payable upon termination or expiration. If terminated under this Article 13, sublicensees may elect to convert their sublicenses to direct licenses with PHS pursuant to Paragraph 4.3. Unless otherwise specifically provided for under this Agreement, upon termination or expiration of this Agreement, Licensee shall return all Licensed Products or other materials included within the Licensed Patent Rights to PHS or provide PHS with certification of the destruction thereof. Licensee may not be granted additional PHS licenses if the final reporting requirement is not fulfilled.

14. GENERAL PROVISIONS

- 14.1 Neither party may waive or release any of its rights or interests in this **Agreement** except in writing. The failure of a party to assert a right hereunder or to insist upon compliance with any term or condition of this **Agreement** shall not constitute a waiver of that right by that party or excuse a similar subsequent failure to perform any of these terms or conditions by the other party.
- 14.2 This **Agreement** constitutes the entire agreement between the parties relating to the subject matter of the **Licensed Patent Rights**, **Licensed Products** and **Licensed Processes**, and all prior negotiations, representations, agreements, and understandings are merged into, extinguished by, and completely expressed by this **Agreement**.
- 14.3 The provisions of this Agreement are severable, and in the event that any provision of this Agreement shall be determined to be invalid or unenforceable under any controlling body of law, this determination shall not in any way affect the validity or enforceability of the remaining provisions of this Agreement.
- 14.4 If either party desires a modification to this **Agreement**, the parties shall, upon reasonable notice of the proposed modification by the party desiring the change, confer in good faith to determine the

desirability of the modification. No modification shall be effective until a written amendment is signed by the signatories to this **Agreement** or their designees.

- 14.5 The construction, validity, performance, and effect of this **Agreement** shall be governed by Federal law as applied by the Federal courts in the District of Columbia.
- 14.6 All **Agreement** notices required or permitted by this **Agreement** shall be given by prepaid, first class, registered or certified mail or by an express/overnight delivery service provided by a commercial carrier, properly addressed to the other party at the address designated on the following Signature Page, or to another address as may be designated in writing by the other party. **Agreement** notices shall be considered timely if the notices are received on or before the established deadline date or sent on or before the deadline date as verifiable by Postal

Service postmark or dated receipt from a commercial carrier. Parties should request a legibly dated Postal Service postmark or obtain a dated receipt from a commercial carrier or the Postal Service. Private metered postmarks shall not be acceptable as proof of timely mailing. Notices can also be sent by an email, or a fax.

- 14.7 This **Agreement** shall not be assigned or otherwise transferred (including any transfer by legal process or by operation of law, and any transfer in bankruptcy or insolvency, or in any other compulsory procedure or order of court) except to **Licensee's Affiliate(s)** without the prior written consent of **PHS**. The parties agree that the identity of the parties is material to the formation of this **Agreement** and that the obligations under this **Agreement** are nondelegable. In the event that **PHS** approves a proposed assignment, **Licensee** shall pay **PHS**, as an additional royalty, one percent (1%) of the fair market value of any consideration received for any assignment of this **Agreement** within sixty (60) days of the assignment.
- 14.8 Licensee agrees in its use of any PHS-supplied materials to comply with all applicable statutes, regulations, and guidelines, including PHS and HHS regulations and guidelines. Licensee agrees not to use the materials for research involving human subjects or clinical trials in the United States without complying with 21 C.F.R. Part 50 and 45 C.F.R. Part 46. Licensee agrees not to use the materials for research involving human subjects or clinical trials outside of the United States without notifying PHS, in writing, of the research or trials and complying with the applicable regulations of the appropriate national control authorities. Written notification to PHS of research involving human subjects or clinical trials outside of the United States shall be given no later than sixty (60) days prior to commencement of the research or trials.
- 14.9 Licensee acknowledges that it is subject to and agrees to abide by the United States laws and regulations (including the Export Administration Act of 1979 and Arms Export Control Act) controlling the export of technical data, computer software, laboratory prototypes, biological material, and other commodities. The transfer of these items may require a license from the appropriate agency of the U.S. Government or written assurances by Licensee that it shall not export these items to certain foreign countries without prior approval of this agency. PHS neither represents that a license is or is not required or that, if required, it shall be issued.
- 14.10 To the extent practicable and allowed by law and regulation, Licensee agrees to mark the Licensed Products or their packaging sold in the United States with all applicable U.S. patent numbers and similarly to indicate "Patent Pending" status. All Licensed Products manufactured in, shipped to, or sold in other countries shall be, to the extent practicable and allowed by law and regulation in such countries, marked in a manner to preserve PHS patent rights in those countries.
- 14.11 By entering into this **Agreement**, **PHS** does not directly or indirectly endorse any product or service provided, or to be provided, by **Licensee** whether directly or indirectly related to this **Agreement**. **Licensee** shall not state or imply that this **Agreement** is an endorsement by the Government, **PHS**,

any other Government organizational unit, or any Government employee. Additionally, **Licensee** shall not use the names of **NIH**, **FDA**, **PHS**, or **HHS** or the Government or their employees in any advertising, promotional, or sales literature without the prior written approval of **PHS**.

- 14.12 The parties agree to attempt to settle amicably any controversy or claim arising under this **Agreement** or a breach of this **Agreement**, except for appeals of modifications or termination decisions provided for in Article 13. Licensee agrees first to appeal any unsettled claims or controversies to the designated **PHS** official, or designee, whose decision shall be considered the final agency decision. Thereafter, Licensee may exercise any administrative or judicial remedies that may be available.
- 14.13 Nothing relating to the grant of a license, nor the grant itself, shall be construed to confer upon any person any immunity from or defenses under the antitrust laws or from a charge of patent misuse, and the acquisition and use of rights pursuant to 37 C.F.R. Part 404 shall not be immunized from the operation of state or Federal law by reason of the source of the grant.
- 14.14 Any formal recordation of this **Agreement** required by the laws of any **Licensed Territory** as a prerequisite to enforceability of the **Agreement** in the courts of any foreign jurisdiction or for other reasons shall be carried out by **Licensee** at its expense, and appropriately verified proof of recordation shall be promptly furnished to **PHS**.
- 14.15 Paragraphs 4.3, 8.1, 9.5-9.7 (in respects of sales carried out prior to termination), 12.1-12.4, 12.5 (in respects of acts carried out prior to termination), 13.9, 13.10, 14.12 and 14.15 of this **Agreement** shall survive termination of this **Agreement**.
- 14.16 The terms and conditions of this **Agreement** shall, at **PHS**' sole option, be considered by **PHS** to be withdrawn from **Licensee**'s consideration and the terms and conditions of this **Agreement**, and the **Agreement** itself to be null and void, unless this **Agreement** is executed by the **Licensee** and a fully executed original is received by **PHS** within sixty (60) days from the date of **PHS** signature found at the Signature Page.

SIGNATURES BEGIN ON NEXT PAGE

PHS PATENT LICENSE AGREEMENT - EXCLUSIVE

SIGNATURE PAGE

IGNALUKE TAGE

/s/ Richard U. Rodriquez Richard U. Rodriguez Director, Division of Technology Development and Transfer Office of Technology Transfer National Institutes of Health

For PHS:

8-5-11 Date Mailing Address or E-mail Address for Agreement notices and reports:

Chief, Monitoring & Enforcement Branch Office of Technology Transfer National Institutes of Health 6011 Executive Boulevard, Suite 325 Rockville, Maryland 20852-3804 U.S.A.

E-mail: LicenseNotices_Reports@mail.nih.gov

For Licensee (Upon, information and belief, the undersigned expressly certifies or affirms that the contents of any statements of Licensee made or referred to in this document are truthful and accurate.)

By:

/s/ Piers Morgan	10 August 2011
Signature of Authorized Official	Date
Piers Morgan	
Chief Financial Officer	
Amsterdam Molecular Therapeutics	
Mailing Address for Agreement notices:	
Chief Executive Officer	
Amsterdam Molecular Therapeutics	

P.O. Box 22506

1100 DA Amsterdam

The Netherlands

Tel. +31(0)20 566 7394

I. Official and Mailing Address for Financial notices (Licensee's contact person for royalty payments)

Piers Morgan

Chief Financial Officer

Amsterdam Molecular Therapeutics

P.O. Box 22506

1100 DA Amsterdam

The Netherlands

Tel.+31(0)20 566 7394

E-mail: p.morgan@amtbiopharma.com

Any false or misleading statements made, presented, or submitted to the **Government**, including any relevant omissions, under this **Agreement** and during the course of negotiation of this **Agreement** are subject to all applicable civil and criminal statutes including Federal statutes 31 U.S.C. §§3801-3812 (civil liability) and 18 U.S.C. §1001 (criminal liability including fine(s) or imprisonment).

APPENDIX A - PATENT(S) OR PATENT APPLICATION(S)

Patent(s) or Patent Application(s):

1. U. S. Patent 6,984,517, issued January 10, 2006, entitled "AAV5 Vector and Uses Thereof; U.S. Patent 7,479,554, issued January 20, 2009, entitled "AAV5 Nucleic Acids" as well as all issued and pending foreign counterparts [**HHS** Ref. No. E-127-1998/0];

2. U. S. Patent 6,855,314, issued February 15, 2005, entitled "AAV5 Vector for Transducing Brain Cells and Lung Cells" [HHS Ref. No. E-072-2000/0].

APPENDIX B - LICENSED FIELDS OF USE AND TERRITORY

I. Licensed Fields of Use:

- (a) Exclusive Licensed Field of Use: (i) Use of the Licensed Patent Rights for the development and sale of AAV5 based therapeutic products to be delivered to the brain or liver for treatment of human diseases originating in the brain or liver; (ii) Note that arthritis related diseases are expressly excluded.
- (b) Non-Exclusive Licensed Field of Use: Use of the Licensed Patent Rights for the development and sale of AAV5 based therapeutic products to treat human diseases other than the ones covered under (a)(i).

II. Licensed Territory:

(a) Worldwide.

APPENDIX C - ROYALTIES

Royalties:

- I. Licensee agrees to pay to PHS a noncreditable, nonrefundable license issue royalty in the amount of one hundred forty thousand dollars (\$140,000). Payment will be made in two tranches, the first payment of one hundred thousand dollars (\$100,000) being payable within sixty (60) days from the effective date of this Agreement; the second payment of forty thousand dollars (\$40,000) being payable on March 1, 2012. If this Agreement is terminated by Licensee on or before March 1, 2012, Licensee agrees to pay the remaining tranch of license issue royalty in full within sixty (60) days before termination
- II. Licensee agrees to pay to PHS a nonrefundable minimum annual royalty in the amount of fifteen thousand dollars (\$15,000) as follows:
 - (a) The first minimum annual royalty is due within sixty (60) days of the effective date of this **Agreement** and may be prorated according to the fraction of the calendar year remaining between the effective date of this **Agreement** and the next subsequent January 1; and
 - (b) Subsequent minimum annual royalty payments are due and payable on January 1 of each calendar year and may be credited against any earned royalties due for sales made in that year.
- III. Licensee agrees to pay PHS earned royalties of one and two-tenth percent (1.2%) on Net Sales by or on behalf of Licensee and its sublicensees.
- IV. Licensee agrees to pay PHS Benchmark royalties within sixty (60) days of achieving each Benchmark :
 - (a) Thirty-one thousand and five hundred U.S. dollars (\$31,500) Initiation of each Phase 1 clinical trial or foreign equivalent.
 - (b) Seventy-eight thousand five hundred U.S. dollars (\$78,500) Initiation of each Phase II clinical trial or foreign equivalent.
 - (c) One hundred and fifty-seven thousand and five hundred U.S. dollars (\$157,500) Initiation of each Phase III clinical trial or foreign equivalent.
 - (d) Initiation of first Marketing Approval or foreign equivalent for any indications in the liver in the following jurisdictions/countries:
 - (i) Three hundred fifteen thousand U.S. dollars (\$315,000) in Europe.
 - (ii) Three hundred fifteen thousand U.S. dollars (\$315,000) in the United States.
 - (iii) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Australia.
 - (iv) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Canada.
 - (v) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Japan.
 - (e) Initiation of first Marketing Approval or foreign equivalent for any indications in the brain in the following jurisdictions/countries:
 - (i) Three hundred fifteen thousand U.S. dollars (S315,000) in Europe.
 - (ii) Three hundred fifteen thousand U.S. dollars (\$315,000) in the United States.
 - (iii) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Australia.
 - (iv) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Canada.
 - (v) Seventy-eight thousand five hundred U.S. dollars (\$78,500) in Japan.

- V. Licensee agrees to pay PHS additional sublicensing royalties, as following, on the fair market value of any consideration received for granting each sublicense within sixty (60) days of the execution of each sublicense:
 - (a) For any sublicense executed by the **Licensee** before the completion of any phase I clinical trial or foreign equivalent for any disease indications, **Licensee** agrees to pay a sublicensing royalty of ten percent (10%); and
 - (b) For any sublicense executed by the Licensee after the completion of any phase I clinical trial or foreign equivalent but before the completion of any phase II clinical trial or foreign equivalent for any disease indications, Licensee agrees to pay a sublicensing royalty of six percent (6%); and
 - (c) For any sublicense executed by the Licensee either after the completion of any phase II clinical trial or foreign equivalent for any disease of Orphan Indication, or after the completion of any phase III clinical trial or foreign equivalent for any other disease indications, whichever comes first. Licensee agrees to pay a sublicensing royalty of three percent (3%).

Contractual payments made by a sublicensee to the **Licensee** or an Affiliate received after the effective date of this **Agreement** for costs, services and expenses for the **Licensee** or Affiliate to conduct, supervise or participate in one or more clinical trial(s) for the development of the **Licensed Products** shall not be accounted for as sublicensing royalties.

APPENDIX D - BENCHMARKS AND PERFORMANCE

Licensee agrees to the following **Benchmarks** for its performance under this **Agreement** and, within thirty (30) days of achieving a **Benchmark**, shall notify **PHS** that the **Benchmark** has been achieved.

Benchmarks for Licensed Products of Orphan Indication (there is no formal Phase III clinical trial required for Marketing Approval) - liver

- I. Initiation of first Phase I clinical trial or foreign equivalent 2012
- II. Initiation of first Phase II clinical trial or foreign equivalent 2014
- III. Submission to Regulatory Authority of first Marketing Approval or foreign equivalent 2015

Benchmarks for Licensed Products - brain

- I. Initiation of Preclinical Development phase or foreign equivalent 2011
- II. Initiation of first Phase I clinical trial or foreign equivalent 2012
- III. Initiation of first Phase II clinical trial or foreign equivalent 2014
- IV. Initiation of first Phase III clinical trial or foreign equivalent 2017
- V. Submission to Regulatory Authority of first Marketing Approval or foreign equivalent 2020

APPENDIX E - COMMERCIAL DEVELOPMENT PLAN

Project Plan Details - Liver:

Acute intermittent porphyria (AIP) is an autosomal dominant inherited condition caused by mutations in the porphobilinogen deaminase (PBGD) gene. The PBGD gene is located on chromosome 11q24.1-24.2 and spread over fifteen exons. The protein encoded by this gene is a rate-limiting enzyme, the PBGD enzyme, in the haem synthetic pathway.

More than 225 mutations of the PBGD gene have been described, all of them associated with loss of catalytic function. The disease shows incomplete penetrance and only 20-50% of persons with one or more of the described mutations exhibit clinical symptoms of the disease. The genetic disorder results in a 50% reduction of PBGD enzymatic activity. This reduction of hepatic PBGD activity leads to an accumulation of toxic metabolites resulting from the blockade within the haem synthesis pathway. Concentrations of haem precursors porphobilinogen (PGB) and delta-aminolevulinic acid (ALA) increase in blood and urine. Lack of haem and/or accumulation of these metabolites are responsible for the acute attacks characteristic of this disease (Kauppinen et al 2005; Herrick and McColl 2005). Currently, there is no treatment available for the disease.

Over the last couple of years **Licensee** has explored AMT-021 (replication defective recombinant adeno-associated viral vector, AAV, containing the porphobilinogen deaminase gene) for therapeutic intervention in AIP. AMT-021 is an AAV with pseudotype 5 capsid, which expresses the human PBGD gene under the transcriptional control of a liver specific promoter. The therapeutic expression cassette consists of the human PBGD cDNA (codon optimised for human expression) inserted downstream of the liver specific promoter EalbAAT and upstream of a human PBGD polyadenylation sequence.

AMT-021 acts by delivering the PBGD expression cassette directly into hepatocytes. The increase of PBGD enzymatic activity in the liver of AIP patients will provide sufficient enzyme to prevent the accumulation of toxic metabolites and thus, prevent porphyric attacks.

The aim of the project is to bring AAV5-PBDG therapy to patients. **Licensee** has already secured orphan designation for AAV5-PBDG treatment for AIP in Europe. The table below describes the outline development plans, starting from a research batch production, and moving through to primate proof-of-concept, tox batch, pre-observational study, product development, GMP production, Phase I/II clinical trial, Phase II/III clinical trial, all the way to regulatory filing. Please note that the timelines are preliminary only, and that it is the nature of scientific and clinical development that planned timelines may change.

The aim of this project is to develop a gene therapy product for the treatment of AIP, and to deliver a data package that is suitable for the submission and approval by the European and North American regulatory authorities.

Vector development and manufacturing

To develop a gene therapy for PBGD deficient patients, AAV5-PBDG product was designed to expresses the human PBGD gene under the control of a liver specific promoter. AAV5-PBDG was produced in insect cells using the recombinant baculovirus method; sufficient amount of material was produced for efficacy studies in mice. Methods to determine the quantity and purity of the rAAV batches were developed. A purification process including chromatography and filtration steps was developed, further optimization and characterization of the scale-up procedure will be performed before a final batch for toxicology, for proof of principle and for clinical trials can be produced.

PoC in pre-clinical models

Because total deficiency of PBGD is lethal in mice, a compound heterozygous mouse (PBGD+/- referred to as AIP mice) with ~35% of normal hepatic PBGD activity, has been developed as an established model to study AIP. This murine model of AIP exhibits, after disease induction with phenobarbital (Pb), the typical biochemical characteristics

of human AIP, notably, decreased hepatic PBGD activity, massively increased urinary excretion of haem precursors (ALA and PBG) and decreased motor function.

AIP mice were used to test the AAV5-PBDG product. The therapeutic effect was evaluated three month after a single intravenous administration of AAV5-PBDG. Efficacy of the therapy was demonstrated as the treatment was able to prevent disease induction with Pb. ALA and PBG levels in treated animals was reduced, and motor disturbance induced by Pb treatment, as measured in the Rotarod test, was almost completely abolished. In addition, PBGD enzymatic activity increased in the AAV5-PBDG treated group 10 times over that of the control group.

This initial PoC will be repeated with the final version of the therapeutic vector following the completion of the vector development and manufacturing optimization. The final PoC will include the following:

PoC in rodent disease model

· PoC in non-human primates, based on agreed protocol

GLP Toxicology

The aim of this section is to deliver toxicology study report suitable for the submission the regulatory authority. The work will entail the following:

- · Scientific advice from a regulatory body (AEMPS and/or EMA) for safety and toxicology package
- · GLP toxicology study in rodents rats or mice, including any required biodistribution studies
- · Supportive data for toxicology study in non-human primates
- GLP germline transmission study

Toxicology study design will take into account:

- · Identification of potential target organs of biological activity and of potential target organs of toxicity
- · Eventual concomitant medication (e.g. immunosuppressants, standard co-medication)
- · Environmental risk/shedding
- · Analysis of appropriateness of surrogate markers of efficacy/safety
- Any other relevant issues as may be identified

Clinical observational, pre-intervention study/studies

Before entering the interventional clinical study, an observation clinical study will be conducted to provide baseline information on the course of the disease by recording episodes AIP, abdominal pain, hospitalizations, extent of any possible known or unknown to be related to AIP symptomatology, incidence of (adverse) clinical events per year, etc. Sufficient data will be collected to provide a clinical picture to obtain a baseline data and to determine how efficacy will be shown during the interventional clinical trial.

Phase I/II

The clinical phase I/II should include an estimated minimum 6 patients that are administered the gene therapy drug, and are followed up and clinically assessed for at least 6 months following drug administration. The primary aim of the clinical study will be safety and efficacy of the AAV5-PBDG product. The clinical trial will include all biochemical, imaging, clinical and functional assays to assess the disease state and change therein over time, the phenotypic disease variation, as well as the overall clinical and psychosocial or other health status or change therein over time of the individual trial subjects, both before, during and following drug administration.

Phase II/III & Regulatory submission

After successful completion of Phase I/II study a Phase II/III trial will be conducted with the aim of bringing the AIP therapy to market. Licensee estimates that 20-30 patients in total would be sufficient for regulatory filing of this product, as AIP is an ultra-orphan disease with a very limited patient number worldwide.

Parkinson's disease (PD) is a progressive neurodegenerative disease, resulting in tremors, stiffness, slowness of movement, and lack of coordination. Patients are faced with a severely debilitating disease and a serious loss in quality of life. PD is caused by degeneration and death of nerve cells in a specific part of the brain known as the substantia nigra. These cells produce dopamine, a substance necessary for communication between nerve cells involved in the coordination of movement.

PD is the second most common neurodegenerative disease. It usually affects people over 65, with an estimated total of 4.5 million patients worldwide. Due to increasing life expectancy of the general population, the number of patients with PD is expected to double to around 9 million patients between now and 2030.

An ideal therapy for PD would decrease disability and slow down or halt disease progression. Unfortunately, such treatments are not available yet and current therapies are limited to symptomatic treatment only. These include levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors and anticholinergic agents.

Glial cell line-derived neurotrophic factor (GDNF) was shown to promote the survival and differentiation of dopaminergic neurons. The therapy aims to protect and enhance the function of the dopamine-producing nerve cells in the brain. To date a number of clinical trials have been conducted in which recombinant GDNF protein has been directly delivered to the PD brain, using a delivery pump device implanted into patients' abdomen. Although the results were inconsistent, due to the difficulty of delivering protein continuously into the brain via an implanted pump, some patients have shown a significant clinical response to the treatment. It is therefore not a question whether this approach works, because it definitely did in some patients, but rather how it can be done more consistently. AAV-GDNF gene therapy treatment would result in continues delivery of GDNF protein into brain, and is therefore likely to result in significant clinical benefit for PD patients.

Licensee has recently started preclinical development of AAV-GDNF gene therapy that will introduce the gene coding for GDNF using recombinant adeno associated virus vector (AAV). AAV serotype 5 has been shown to be the serotype of choice for gene delivery into the brain. After successful proof of concept (POC) and toxicology studies in rodents and primates, AMT will start an extensive clinical development.

The aim of this project is to develop a gene therapy product for the treatment of Parkinson's disease, and to deliver a data package that is suitable for the submission and approval by the European and North American regulatory authorities.

Vector development and manufacturing

To develop a gene therapy for Parkinson's disease, AAV-GDNF product was designed to expresses the human GDNF and is produced in insect cells using the recombinant baculovirus method. The AAV5-GDNF is based on **Licensee**'s standard manufacturing process, but in addition incorporates recent new technology of the basic process and makes use of an optimized Rep baculovirus construct in the upstream process and an additional chromatography step in the downstream process. This optimisation delivers enhanced quality and robustness of the AAV5-GDNF product. This process is fully scalable and allows for manufacturing of sufficient GMP-compliant product for PD patients.

Characterization of AAV5-GDNF

The AAV5-GDNF was tested in a functional in vitro assay in cultured E13.5 rat DRG explants. Vigorous neural outgrowth was observed, indicating that the produced AAV5-GDNF is capable of mediating secretion of biologically functional recombinant GDNF.

In vivo characterization

Subsequently, an in-vivo characterisation of the AAV5-GDNF has been conducted. Three different concentrations of AAV5-GDNF were injected unilaterally into the rat striatum. Brains were analyzed for GDNF expression 6 weeks post injection using immunohistochemistry. Resulting data demonstrated that there is a strong, concentration dependent GDNF expression throughout the injected hemisphere.

PoC in pre-clinical models

The produced AAV5-GDNF will be used to show biological activity and efficacy in animal models of Parkinson's disease. These experiments will be conducted using rat models of Parkinson's disease (in collaboration with University of Lund, Sweden) as well as non-human primates' model of Parkinson's disease (in collaboration with CEA, Paris, France). In addition to distribution studies, onset and kinetics of GDNF expression, neurochemical measurements (dopamine and dopamine metabolites), immunohistochemistry and behavioral studies will be conducted to test for functional improvement.

GLP Toxicology

The definitive design of the actual studies will be finalized after discussions with relevant agencies. **Licensee** proposes to conduct a six months study in mice and in parallel a 6-12 months study in non-human primates to account for the safety of the drug. The studies will comprise four test groups: 1. Control (vehicle), 2. Low dose (No observed effect level (NOEL) in the proof-of concept studies), 3. Mid-dose (highest dose considered for clinical studies), and 4. High dose (10 times higher than the mid-dose).

The protocol will include the following evaluations:

- · Clinical Signs: recorded daily, beginning 7 days prior to surgery
- · Food Consumption: recorded daily, beginning 7 days prior to surgery
- · Body Weight: Once pre-surgery, day of surgery, then bi-weekly
- · Clinical Chemistry: Twice a month presurgery, one week post surgery, then monthly
- · Hematology: Twice a month presurgery, one week post surgery, then monthly
- · Coagulation: Twice a month presurgery, one week post surgery, then monthly
- · Antibodies against GDNF or AAV5 in plasma, twice prior to surgery, monthly thereafter.
- · PK CSF: To determine if there is GDNF in the CSF, twice prior to surgery, monthly thereafter.
- · Neurological Examination: Twice prior to surgery, Day 7 post surgery, monthly thereafter
- MRI (T1,T2): Once prior to surgery, within three hours post surgery, and within three days prior to necropsy.
- Pathology
- 1. Gross pathology at necropsy
- 2. Selected peripheral tissues collected for histopathological analysis by a Board Certified Pathologist
- 3. Complete CNS histopathological assessment by a Board Certified Neuropathologist, peer reviewed by another Board Certified Pathologist

Q-PCR in selected organs in order to assess any biodistribution of the vector DNA to other organs.

Phase I/II

The primary objective of the clinical phase I/II will be to assess the safety and feasibility of intra-putaminal delivery of AAV5-GDNF to patients with PD. Secondary objectives include measuring clinical efficacy and demonstrating improvement in a surrogate marker end point (18F-Dopa PET) as proof of concept.

Licensee is proposing a single centre open label trial of striatally delivered AAV5-GDNF in PD employing a dose escalation design to assess the mentioned primary and secondary outcome measures. Licensee anticipates enrolling 12 patients in this study, with an escalating dose group design with three patients in each dose group. Licensee will start with the lowest dose and progress in an incremental way to higher doses.

Primary outcome assessments will be performed at two weeks, one month, three months, six months, 12 months and 18 months post intra-putaminal infusion of AAV5-GDNF. Clinical secondary outcome assessments will be performed at three months, six months, 12 months and 18 months post intra-putaminal infusion of AAV5-GDNF. 18F-dopa PET secondary outcome assessments will be performed at six months and 18 months post intra-putaminal infusion of AAV5-GDNF.

If feasibility and safety is confirmed and, serial PET imaging demonstrates increased 18F-dopa uptake with a trend towards clinical improvement, we will proceed to phase 2/3 clinical trials.

Phase II/III, Phase III & Regulatory submission

After successful completion of Phase I/II study, two additional clinical trials will be required. The final plans for these trials will be optimized based on the outcome of the Phase I/II study. **Licensee** estimates 50 patients to be enrolled in the Phase II/III clinical study, and 500 patients to be enrolled in the pivotal trial, the details however will be established, based on the outcome of the Phase I/II trial.

Additional indication;

In addition to the above, **Licensee** has an active programs in hemophilia B using AAV5-Factor IX, in hemophilia A using AAV5-Factor VIII, in Sanfilippo B - currently conducted by Institut Pasteur, using AAV5-NaGlu gene, and a program for the development of treatment for Usher syndrome type 1 (USH1) using AAV5-MY07A. Additional early stage programs are under evaluation.

APPENDIX F - EXAMPLE ROYALTY REPORT

Required royalty report information includes:

- · OTT license reference number (L-XXX-200X/0)
- · Reporting period
- · Catalog number and units sold of each Licensed Product (domestic and foreign)
- · Gross Sales per catalog number per country
- · Total Gross Sales
- · Itemized deductions from Gross Sales
- Total Net Sales
- Earned Royalty Rate and associated calculations
- · Gross Earned Royalty
- · Adjustments for Minimum Annual Royalty (MAR) and other creditable payments made
- · Net Earned Royalty due

Example

Catalog Number	Product Name	Country	Units Sold	(US\$)
1	A	US	250	62,500
1	Α	UK	32	16,500
1	А	France	25	15,625
2	В	US	0	0
3	С	US	57	57,125
4	D	US	12	1,500
			Total Gross Sales	153,250
			Less Deductions:	
			Freight	3,000
			Returns	7,000
			Total Net Sales	143,250
			Royalty Rate	8%
			Royalty Due	11,460
			Less Creditable Payments	10,000
			Net Royalty Due	1,460

APPENDIX G - ROYALTY PAYMENT OPTIONS

The OTT License Number MUST appear on payments, reports and correspondence.

Automated Clearing House (ACH) for payments through U.S. banks only

The NIH encourages our licensees to submit electronic funds transfer payments through the Automated Clearing House (ACH). Submit your ACH payment through the U.S. Treasury web site located at: https://www.pay.gov. Locate the "NIH Agency Form" through the Pay.gov "Agency List".

Electronic Funds Wire Transfers

The following account information is provided for wire payments. In order to process payment via Electronic Funds Wire Transfer sender MUST supply the following information within the transmission:

Drawn on a U.S. bank account via FEDWIRE should be sent directly to the following account:

Beneficiary Account:	Federal Reserve Bank of New York or TREAS NYC
Bank:	Federal Reserve Bank of New York
ABA#	021030004
Account Number:	75080031
Bank Address:	33 Liberty Street, New York, NY 10045
Payment Details:	License Number (L-XXX-XXXX)
-	Name of Licensee

Drawn on a **foreign bank account** should be sent directly to the following account. Payment must be sent in **U.S. Dollars (USD)** using the following instructions:

Beneficiary Account:	Federal Reserve Bank of New York/ITS or FRBNY/ITS
Bank:	Citibank N.A. (New York)
SWIFT Code:	CITIUS33
Account Number:	36838868
Bank Address:	388 Greenwich Street, New York, NY 10013
Payment Details (Line 70):	NIH 75080031
	License Number (L-XXX-XXXX)
	Name of Licensee
Detail of Charges (line 71a):	Charge Our

Checks

All checks should be made payable to "NIH Patent Licensing"

Checks drawn on a U.S. bank account and sent by US Postal Service should be sent directly to the following address:

National Institutes of Health (NIH) P.O. Box 979071 St. Louis, MO 63197-9000

Checks drawn on a U.S. bank account and sent by overnight or courier should be sent to the following address:

US Bank Government Lockbox SL-MO-C2GL 1005 Convention Plaza St. Louis, MO 63101 Phone: 314-418-4087

Checks drawn on a foreign bank account should be sent directly to the following address:

National Institutes of Health (NIH) Office of Technology Transfer Royalties Administration Unit 6011 Executive Boulevard Suite 325, MSC 7660 Rockville, Maryland 20852

NATIONAL INSTITUTES OF HEALTH

FIRST AMENDMENT TO L-116-2011/0

This is the first amendment ("First Amendment") of the agreement by and between the National Institutes of Health ("NIH") within the Department of Health and Human Services ("HHS"), and UniQure biopharma B.V. (formerly Amsterdam Molecular Therapeutics N.V. (AMT)) having an effective date of August 10, 2011 and having NIH Reference Number L-116-2011/0 ("Agreement"). This First Amendment, having NIH Reference Number L-116-2011/1, is made between the NIH through the Office of Technology Transfer, NIH, having an address at 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804, U.S.A., and UniQure biopharma B.V. (formerly Amsterdam Molecular Therapeutics N.V. (AMT)), having an office at Meibergdreef 61, 1105 BA

Amsterdam, The Netherlands ("Licensee"). This First Amendment includes, in addition to the amendments made below, 1) a Signature Page, and 2) Attachment 1 (Royalty Payment Information).

WHEREAS, NIH and Licensee desire that the Agreement be amended a first lime as set forth below in order to

- a) Change the name of **Licensee** from Amsterdam Molecular Therapeutics N.V. (AMT) to UniQure biopharma B.V. (UniQure). This name change is the result of a transaction that took place on 30 March 2012, whereby AMT, a public company, was liquidated and all its operations and stocks were transferred to UniQure, a privately held company.
- b) Modify language related to financial terms associated with sublicensing, so as to cause a reduction in financial obligations due to **NIH** from sublicensing of the **Agreement** by **Licensee** in order to expedite the development of therapeutics for rare diseases.

NOW, THEREFORE, in consideration of the mutual covenants and promises contained herein, **NIH** and **Licensee**, intending to be bound, hereby mutually agree to the following:

- 1) a) In Cover page following the list of "licensed patent and patent application", the name of Licensee has been changed to UniQure biopharma B.V.
 - b) In the signature page under "signature of authorized official", under "mailing address for **Agreement** notices", and under "official and mailing address for financial notices" "Amsterdam Molecular Therapeutics, N.V." has been changed to UniQure biopharma B.V.
 - c) In the caption of the Agreement AMT is changed to UniQure.
- 2) Replace Paragraph 6.7 with the following:
 - 6.7 No multiple royalties shall be payable if any Licensed Products or Licensed Processes are covered by more than one of the Licensed Patent Rights. In the event that this Agreement and NIH license L-107-2007/0 as amended from time to time apply to the same product sold by the Licensee or its sublicensees, then the Licensee shall only pay earned royalties, benchmark royalties, and sublicensing royalties under this Agreement.
- 3) Replace Appendix C Section V with the following:

Licensee agrees to pay NIH additional sublicensing royalties, as follows, on the fair market value of any consideration received for granting each sublicense within sixty (60) days of the execution of each sublicense:

(i) For any sublicense executed by the **Licensee** before the completion of any phase I clinical trial or foreign equivalent for any disease indication, **Licensee** agrees to pay a sublicensing royalty as in the following formula:

Sublicensing Royalty = 10.0% x P/(P+T+L)

for the purposes of calculating sublicensing royalties in (i), where P/(P+T+L) is a fraction in which P represents the **NIH's Licensed Patent Right**, T represents the Intellectual Property (IP) licensed by Licensee from a third party, and where such an IP is related only to an active component of the **Licensed Products** (i.e. gene of interest incorporated into the AAV construct), and L represents **Licensee's** own IP used to make the **Licensed Product**. Furthermore P, T and L, when present, each carries a value of 1. The value of the fraction P/(P+T+L) as applied to (i) can never go below 1/3 (0.33), and therefore the Sublicensing Royalty as applied to (i) will never go below 3.3% (10.0% x 0.33).

(ii) For any sublicense executed by the Licensee after the completion of any phase 1 clinical trial or foreign equivalent but before the completion of any phase II clinical trial or foreign equivalent for any disease indication, Licensee agrees to pay a sublicensing royalty as in the following formula:

Sublicensing Royalty =6.0% x P/(P+T+L)

The value of the fraction P/(P+T+L) as applied to (ii) can never go below 0.45, and therefore the Sublicensing Royalty as applied to (ii) will never go below 2.7% (6.0% x 0.45)

(iii) For any sublicense executed by the Licensee either after the completion of any phase II clinical trial or foreign equivalent for any disease of Orphan Indication, or Ultra-Orphan Indication, or after the completion of any phase III clinical trial or foreign equivalent for any other disease indications, Licensee agrees to pay a sublicensing royalty as in the following formula:

Sublicensing Royalty = 3.0% x P/(P+T+L)

The value of the fraction P/(P+T+L) as applied to (iii) can never go below 0.65, and therefore the Sublicensing Royalty as applied to (iii) will never go below 1.95% (3.0% x 0.65)

Contractual payments made by a sublicensee to the Licensee or an Affiliate received after the effective date of this Agreement for costs, services and expenses for the Licensee or Affiliate to perform research and development activities, or to conduct, supervise or participate in one or more clinical trial(s) for the development of the Licensed Products, or to manufacture clinical and commercial batches of Licensed Products, shall not be accounted for in the calculation of sublicensing royalties.

- 4) Licensee shall pay NIH an amendment issue royalty in the sum of five hundred thousand US Dollars (\$500,000.00) as follows:
 - i) Two hundred and fifty thousand Dollars (\$250,000) shall be paid by Licensee within sixty (60) days of the effective date of this First Amendment.

- ii) The remaining amount of two hundred and fifty thousand Dollars (\$250,000) shall be paid to **NIH** upon execution by **Licensee** of any new sublicensing or partnership agreement or on the first anniversary of this **First Amendment**, whichever occurs first.
- 5) In the event any provision(s) of the **Agreement** is/are inconsistent with Attachment 1, such provision(s) is/are hereby amended to the extent required to avoid such inconsistency and to give effect to payment information in such Attachment 1.
- 6) All terms and conditions of the Agreement not herein amended remain binding and in effect.
- 7) The terms and conditions of this First Amendment shall, at NIH' sole option, be considered by NIH to be withdrawn from Licensee's consideration and the terms and conditions of this First Amendment, and the First Amendment itself, to be null and void, unless this First Amendment is executed by Licensee and a fully executed original is received by NIH within sixty (60) days from the date of NIH signature found at the Signature Page.
- 8) This **First Amendment** is effective on upon execution by all parties.

FIRST AMENDMENT TO L-116-2011/0

SIGNATURE PAGE

In Witness Whereof, the parties have executed this **First Amendment** on the dates set forth below. Any communication or notice to be given shall be forwarded to the respective addresses listed below.

For NIH:

/s/ Richard U. Rodriguez	5-23-13
Richard U. Rodriguez	Date
Director, Division of Technology Development and Transfer	
Office of Technology Transfer	
National Institutes of Health	

Mailing Address or E-mail Address for Agreement notices and reports:

Chief, Monitoring & Enforcement Branch, DTDT Office of Technology Transfer National Institutes of Health 6011 Executive Boulevard, Suite 325 Rockville, Maryland 20852-3804 U.S.A.

E-mail: LicenseNotices_Reports@mail.nih.gov

For Licensee (Upon information and belief, the undersigned expressly certifies or affirms that the contents of any statements of Licensee made or referred to in this document are truthful and accurate.):

/s/ John Alday	5-31-13
John Alday, CEO UniQurebiopharm B.V.	Date

I.	Official and Mailing Address for Agreement notices:
	Chief Executive Officer:
	Legal@uniqure.com

II. For invoices, payments, and Financial notices (including royalty payments): Finance Dept *Finance@uniqure.com*

uniQure biopharma B.V. Meibergdreef 61 1105BA Amsterdam The Netherlands

Phone:0031 205667394Fax:0031 20 566 9272

Any false or misleading statements made, presented, or submitted to the **Government**, including any relevant omissions, under this **Agreement** and during the course of negotiation of this **Agreement** are subject to all applicable civil and criminal statutes including Federal statutes 31 U.S.C. §§3801-3812 (civil liability) and 18 U.S.C. §1001 (criminal liability including fme(s) or imprisonment).

ATTACHMENT 1 - ROYALTY PAYMENT OPTIONS

Automated Clearing House (ACH) for payments through U.S. banks only

The NIH encourages our licensees to submit electronic funds transfer payments through the Automated Clearing House (ACH). Submit your ACH payment through the U.S. Treasury web site located at: https://www.pay.gov. Locate the "NIH Agency Form" through the Pay.gov "Agency List".

Electronic Funds Wire Transfers

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Drawn on a U.S. bank account via FEDWIRE should be sent directly to the following account:

Beneficiary Account:	Federal Reserve Bank of New York or TREAS NYC
Bank:	Federal Reserve Bank of New York
ABA#	021030004
Account Number:	75080031
Bank Address:	33 Liberty Street, New York, NY 10045
Payment Details:	License Number (L-XXX-XXXX)
	Name of Licensee

Drawn on a **foreign bank account** should be sent directly to the following account. Payment must be sent in **U.S. Dollars (USD)** using the following instructions:

Beneficiary Account:	Federal Reserve Bank of New York/ITS or FRBNY/ITS
Bank:	Citibank N.A. (New York)
SWIFT Code:	CITIUS33
Account Number:	36838868
Bank Address:	388 Greenwich Street, New York, NY 10013
Payment Details (Line 70):	NIH 75080031
	License Number (L-XXX-XXXX)
	Name of Licensee
Details of Charges (Line 71a):	Charge Our

Checks

All checks should be made payable to "NIH Patent Licensing"

Checks drawn on a U.S. bank account and sent by US Postal Service should be sent directly to the following address:

National Institutes of Health (NIH) P.O. Box 979071 St. Louis, MO 63197-9000

Checks drawn on a U.S. bank account and sent by overnight or courier should be sent to the following address:

US Bank Government Lockbox SL-MO-C2GL 1005 Convention Plaza St. Louis, MO 63101 Phone: 314-418-4087

Checks drawn on a foreign bank account should be sent directly to the following address:

National Institutes of Health (NIH) Office of Technology Transfer Royalties Administration Unit 6011 Executive Boulevard Suite 325, MSC 7660 Rockville, Maryland 20852

NATIONAL INSTITUTES OF HEALTH SECOND AMENDMENT TO L-116-2011/0

This is the second amendment ("Second Amendment") of the agreement by and between the National Institutes of Health ("NIH") within the Department of Health and Human Services ("HHS"), and UniQure biopharma B.V. (formerly Amsterdam Molecular Therapeutics (AMT) B.V.) having an effective date of August 10, 2011 as amended for the first time on May, 31, 2013, and having NIH Reference Number L-116-2011/0 and L-116-2011/1 respectively ("Agreement"). This Second Amendment, having NIH Reference Number L-116-2011/2, is made between the NIH through the Office of Technology Transfer, NIH, having an address at 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804, U.S.A., and UniQure biopharma B.V. (formerly Amsterdam Molecular Therapeutics (AMT) B.V.), having an office at Meibergdreef 61, 1105 BA Amsterdam, The Netherlands ("Licensee"). This Second Amendment includes, in addition to the amendments made below, a Signature Page.

WHEREAS, NIH and Licensee desire that the Agreement be amended a second time as set forth below in order to a) clarify the nonexclusive Field of Use, b) to update appendices D and E of the Agreement, and c) to update Article 6.13 of the Agreement with the name of an Exempt Collaborator that is approved to work with the Licensee on one Ultra-Orphan Indication.

NOW, THEREFORE, in consideration of the mutual covenants and promises contained herein, NIH and Licensee, intending to be bound, hereby mutually agree to the following:

- 1) In Appendix B replace Paragraph I(b) of the Licensed Field of Use with the following:
 - (b) Non-Exclusive Licensed Field of Use: Use of the Licensed Patent Rights for the development and sale of AAV5 based therapeutic products to treat any human disease in any manner, where the treatment of such disease in such manner is not included in the Exclusive Licensed Field of Use.
- 2) In Article 6.13 add the following:
 - Institut Pasteur has been approved by the NIH as an Exempt Collaborator for a clinical work related to Sanfilippo B. (h)
- 3) Replace Appendix D with Appendix D attached to this Second Amendment as EXHIBIT 1.
- 4) Replace Appendix E with Appendix E attached to this Second Amendment as EXHIBIT 2.
- 5) All terms and conditions of the Agreement not herein amended remain binding and in effect.
- 6) The terms and conditions of this Second Amendment shall, at NIH sole option, be considered by NIH to be withdrawn from Licensee's consideration and the terms and conditions of this Second Amendment, and the Second Amendment itself, to be null and void, unless this Second Amendment is executed by Licensee and a fully executed original is received by NIH within sixty (60) days from the date of NIH signature found at the Signature Page.
- 7) This Second Amendment is effective on the date of execution by the last party to execute this Second Amendment.

SECOND AMENDMENT TO L-116-2011/0

SIGNATURE PAGE

In Witness Whereof, the parties have executed this Second Amendment on the dates set forth below. Any communication or notice to be given shall be forwarded to the respective addresses listed below.

For NIH:

/s/ Richard U. Rodriguez	11-6-13
Richard U. Rodriguez	Date
Director, Division of Technology Development and Transfer	
Office of Technology Transfer	
National Institutes of Health	

Mailing Address or E-mail Address for Agreement notices and reports:

Chief, Monitoring & Enforcement Branch, DTDT Office of Technology Transfer National Institutes of Health 6011 Executive Boulevard, Suite 325 Rockville, Maryland 20852-3804 U.S.A.

E-mail: LicenseNotices Reports@mail.nih.gov

For Licensee (Upon information and belief, the undersigned expressly certifies or affirms that the contents of any statements of Licensee made or referred to in this document are truthful and accurate.):

/s/ Piers J. Morgan P.J. Morgan Piers J Morgan, CFO, uniQure biopharma B.V. Date Official and Mailing Address for Agreement notices: I Chief Executive Officer; Legal@uniqure.com Π For invoices, payments, and Financial notices (including royalty payments): Finance Dept Finance@uniqure.com uniQure biopharma B.V. Meibergdreef 61 1105BA Amseterdam The Netherlands Phone: 0031 205667394 Fax: 0031 20 566 9272

November 11, 2013

Any false or misleading statements made, presented, or submitted to the **Government**, including any relevant omissions, under this **Agreement** and during the course of negotiation of this **Agreement** are subject to all applicable civil and criminal statutes including Federal statutes 31 U.S.C. §§3801-3812 (civil liability) and 18 U.S.C. §1001 (criminal liability including fine(s) or imprisonment).

Exhibit 1

APPENDIX D - BENCHMARKS AND PERFORMANCE (L-116/2011)

Licensee agrees to the following **Benchmarks** for its performance under this **Agreement** and, within thirty (30) days after achieving a **Benchmark**, shall notify **PHS** that the **Benchmark** has been achieved.

Note: No formal Phase III clinical trial is required for Marketing Approval for any Orphan Indication

Benchmarks for a Licensed Product of Orphan Indication - liver

- I. Initiation of first Phase I clinical trial or foreign equivalent 2012
- II. Initiation of first Phase II clinical trial or foreign equivalent 2016
- III. Submission to Regulatory Authority of first Marketing Approval or foreign equivalent 2018

Benchmarks for a Licensed Product - brain

- I. Initiation of Preclinical Development phase or foreign equivalent 2011
- II. Initiation of first Phase I clinical trial or foreign equivalent 2013
- III. Initiation of first Phase II clinical trial or foreign equivalent 2016
- IV. Submission to Regulatory Authority of first Marketing Approval or foreign equivalent —2018

Exhibit 2

APPENDIX E - COMMERCIAL DEVELOPMENT PLAN (L-116-2011)

The table below (table 1) presents a comprehensive list of all uniQure research and development projects utilizing the Licensed Patent Rights, according to main disease site and divided into projects that are, **a**) commercial projects, **b**) already in development stages, **c**) active research (there is already internal research activity ongoing and **d**) exploratory research projects (currently being considered as potential projects worth further investigation in the near future).

Table 1: uniQure R&D projects

	Liver (AAV5 based)	Brain & CNS (AAV5 based)
Commercial	_	
Projects		
Development Projects	Acute Intermittent Porphyria (AMT-021)	 Sanfilippo B (MPS IIIB)
	· Hemophilia B (AMT-060)	(AMT-110)
Active Research Projects	• Hemophilia A (HA)	 Huntington's Disease
	· Cirrhosis	 Multiple System Atrophy (MSA)
	 Hyperoxalurea (HP1) 	· Hearing loss
Exploratory Research Projects	· Phenylketonuria (PH1)	· Amyotrophic lateral sclerosis (ALS - motor
	Ornithine transcarbamylase deficiency	neurone disease or Lou Gehrig's disease)
	(OTCD)	· Spinal muscular atrophy (SMA)
	· Glycogen storage disease type II (Pompe)	· Batten's disease
	· Maroteaux-Lamy syndrome (MPS VI)	 Tay Sachs
	• Fabry disease	• Krabbe disease (globoid cell leukodystrophy or galactosylceramide lipidosis)

Detailed information on the development and active research projects is provided below. **NOTE: All dates contained in this Commercial Development Plan are projected estimates only.**

Liver Programs

A) Development Programs

- 1. AMT-021 for Acute Intermittent Porphyria
 - 1.1.1 Disease Background

Acute Intermittent Porphyria, or AIP, is a rare liver metabolic disorder resulting from mutations in the PBGD gene. This gene encodes for the enzyme porphobilinogen deaminase (also known as hydroxymethylbilane synthase — HMBS), a liver protein necessary for the production of heme, a component of hemoglobin and other blood proteins. Insufficient activity of this protein leads to an accumulation of toxic metabolites (ALA and PBG), resulting in a wide variety of serious clinical problems, including acute, severe abdominal pain, muscular weakness and an array of neurologic manifestations, including psychiatric episodes, seizures and coma. In the majority of cases, attacks are triggered by precipitating factors such as hormonal fluctuations, infections, drugs and dietary changes. Long-term consequences may include irreversible nerve damage, liver cancer and kidney failure. Patients with AIP experience regular hospitalizations and extremely poor quality of life, and may in some cases require liver transplants. Acute attacks can be life-threatening. Current therapies only target the disease symptoms and do not prevent attacks or fully minimize or control their consequences.

A recent epidemiological study reported that, in Europe (excluding Sweden), the incidence of AIP is 0.13 per million population per year and based on that they estimated a prevalence of 5.9 per million population (Elder et al., 2012). In Sweden the incidence and prevalence of AIP are about four times higher than in the rest of Europe due to a founder effect originating in Lappland (Floderus et al., 2002). The frequency in the United States is estimated to be 1-5 cases per 100,000 population (www.emedicine.medscape.com/article/205220-overview#a0199).

1.1.2 Overview of AMT-021 Program

The goal of our AMT-021 program is to provide long-term normalization of the PBGD protein in order to prevent acute AIP attacks and their complications.

The program has been developed through a collaborative agreement with the Foundation for Applied Medical Research (FIMA), its Center for Applied Medical Research (CIMA) and its commercialization arm, DIGNA Biotech, of the University of Navarra (Pamplona, Spain). Part of the funding to support for the Phase I trial (including GLP safety & toxicology studies and the observational trial) was secured through the European Commission Framework Programme 7 award (€3.3 million, grant agreement 261506) made to the AIPGENE consortium (www.aipgene.org/), of which uniQure is a partner.

UniQure holds an exclusive license to the gene cassette being used in the Phase I clinical trial. Under our agreement with DIGNA Biotech and the other consortium members, Licensee have an exclusive right to all data related to the program.

- 1.1.3 Preclinical Development
- Product Profile
 - 1.1.4 *AMT-021 is designed to be delivered systemically through a peripheral vein in a single administration.*

AMT-021 or rAAV5-hPBGD, is a recombinant adeno-associated vector of serotype 5, consisting of:

- · Inverted terminal regions or ITRs of the adeno-associated serotype 2
- · A human codon optimized porphobilinogen deaminase gene or hPBGDco as the therapeutic gene
- · A liver specific promoter constituted by the albumin enhancer (Ealb) and the alfa-1-antitrypsin promoter (hAAT)

1.1.5

Pre-clinical Proof of Concept

1.1.6 Pre-clinical proof of concept (PoC) studies have been performed using the AIP murine model developed by Lindberg et al. (1999). In these studies, long term therapeutic efficacy was achieved. More specifically, at 5x10¹³ gc/kg, metabolic correction of the hepatic PBGD enzyme activity, normalization of the PBG and ALA precursor's accumulation in urine and improvement of the motor coordination were observed. Additionally, a complete neurological study indicated the correction of neurotoxic porphyrin precursors was able to restore nerve conduction and the impaired peripheral neuropathy.

In non-human primates (NHP) treated with AMT-021 at a dose of $5x10^{13}$ gc/kg endogenous PBGD enzymatic activity increased by a factor of two in male and between three and five times in female animals.

Non-clinical safety & toxicology studies

1.1.7 The following table presents a summary of the AMT-021 non-clinical safety and toxicology studies that have been conducted to support the clinical development program.

Parameter to be assessed	Study performed	Results
Pharmacokinetics	1) GLP biodistribution in C57Bl/6 mice (180	In both species,
	days) with validated QPCR method.	 Clear correlation between the dose of vector administered and the genome copies of the vector as well as vector RNA (expression)
	2) Biodistribution data in Rhesus macaques	quantified in the liver.
	(supportive)	 Tissue biodistribution was mainly limited to liver although some significant transduction was detected in spleen, lymph nodes, heart and adrenal glands.
Toxicity	1) GLP toxicity study in Rhesus macaques, 30	In Rhesus macaques:
	days	 No specific macroscopic or microscopic findings, no severe immune/inflammatory reactions (NOAEL 5x10¹³ gc/kg)
	2) GLP toxicity study in C57Bl/6 mice (180 days)	In C57Bl/6 mice:
		 No severe adverse toxicologically significant findings
		• At highest dose limited hepatocyte vacuolation due to metabolic adaptation to high PBGD activity in liver (NOAEL 5x10 ¹⁴ gc/kg)

Off-target expression Shedding pattern Persistence in semen and risk of germline	Included in the GLP toxicity study in monkey and mouse Included in the Rhesus macaques study Mouse Germline transmission study in C57Bl/6 mice	Vector RNA analysis for all tissues other than liver showed that there is no PBGD transcription and translation elsewhere. Shedding in semen and saliva is transient (cleared by day 30) No transmission to offspring
transmission Carcinogenicity	Analyze tissues from the Rhesus studies using LAM-PCR	 Low frequency of integration sites, with random distribution No preferences for CpG islands No preference for palindromic regions No hotspots (low clustering level)

1.1.8 Summary of AMT-021 Preclinical Development Program

Single intravenous administration of AMT-021 into wild type mice and Rhesus macaques results in:

- Efficient liver transduction resulting in dose dependent increase in viral RNA copy numbers and in turn producing increased PBGD activity
- No morbidity, no changes in body weight or food intake
- No changes in biochemistry, hematology, coagulation and urinalysis associated with AAV5-hPBGD
- Negative vector shedding 30 days after viral administration in serum, saliva, nasal secretions, urine, faeces and semen
- Tissue biodistribution that is mainly limited to liver although some significant transduction was detected in spleen, lymph nodes, heart and adrenal glands
- Specific hepatic PBGD expression
 - 1.1.9 Clinical Development Program
 - 1.1.10 The key regulatory and clinical development best estimate milestones for AMT-021 include the following,

	EMA Orphan Drug Designation (EU/3/09/632)		Apr 2009
	FIMA/ CITA/ UTE/ DIGNA - AMT Collaborative Agreement		May 2010
·	EU-FP7 AIPGene Consortium		Jan 2011
	Observational Study AEMPS approval		May 2011
	Observational Study start		Jul 2011
	Phase I Study AEMPS approval		Oct 2012
	Phase I Study: first patient treated		Dec 2012
	Phase I Study: last patient treated		Aug 2013
spected n	nilestones		
	Phase II/III start:	402016	
	MAA/ NDA submission:	4Q2010	
	Observational trial		202018

1.1.11 A prospective non-interventional (pre-treatment) observational study started at the end of 2011 that aims to assess the evolution of disease-related clinical and laboratory parameters in time, as well as characterize aspects of disease management such as AIP-related hospitalization. This baseline assessment is intended to study possible relationships between biochemical parameters and clinical endpoints that will in turn be valuable in evaluating any signs of efficacy in the Phase I trial as well as in subsequent trials. Eight patients are expected to be enrolled who after completion of this observational phase would then enter the interventional stage of the program, i.e., first-in-human clinical study (Phase I). The observational study is to last for at least six months for each participant.

1.1.12 To date all 8 AIP-patients have been recruited into the observational study and all but one have completed a minimum of 6 months pretreatment assessments. The last patient completed the observational study in August 2013.

· Phase I trial

E

1.1.13 The Investigational Medicinal Product Dossier (IMPD) was submitted to the AEMPS (Spanish Agency for Medicines and Medical Devices) in June 2012 and was approved by the Agency in October 2012.

The Phase I study is a multicenter, open label, prospective, interventional, single dose, dose-escalation clinical trial to investigate the safety and tolerability of AAV5-hPBGDco (AMT-021) in patients with severe Acute Intermitted Prophyria (Eudra CT no. 2011-005590-23).

The primary objective is to assess the safety of systemic administration and determine the maximum tolerated doses (MTD). Secondary objectives include urinary levels of toxic metabolites (ALA and PBG), disease symptoms evaluation, quality of life evaluation and assessment of pharmacokinetics. Exploratory objectives include, neurological involvement, identification of novel biomarkers and pharmacokinetic modeling.

The Phase I study was initiated in December 2012 in the Department of Medicine (Liver Unit) at the University Clinic of the University of Navarra (Pamplona, Spain). There are two patients per cohort and four cohorts in the trial (each cohort receiving $5x10^{11}$, $2x10^{12}$, $6x10^{12}$ or $1.8x10^{13}$ gc/kg) and all patients will be followed- up for one year as part of the Phase I study.

All 8 patients who completed the observational trial have also been treated as part of the Phase I study. In the 8 treated patients, no Serious Adverse Events, Treatment Emergent Adverse Events or Liver Events (Dose Limiting Toxicities - DLT's) related to the study medication have been observed to date.

· Future Clinical Development

It is envisaged that the Phase II/III will be a confirmatory trial where the study population and the outcomes to be assessed (efficacy endpoints — clinical and biochemical) will be based on those as for Phase I. **Licensee** also intend to carry out the study in both Europe and the USA.

1.1.14 Summary of AMT-021 Clinical Development Program

- · The first time an AAV5 gene therapy product has been tested in humans
- The first time an AAV gene therapy product has been tested in humans at such high dose, i.e., 1.8x10¹³ gc/kg
- No Serious Adverse Events, Treatment Emergent Adverse Events or Liver Events (DLT's) related to the study medication have been observed in the Phase I study to date
- The Phase I is expected to be completed in 3Q14 and Phase II/III is expected to start by the end of 2014
- The Phase II/III program will run in parallel in Europe and US where MAA and NDA, respectively, are expected in 4Q2016
- 2. AMT-060 for Hemophilia B

1.1.1 Disease Background

Hemophilia B is a serious inherited orphan disease in males characterized by insufficient blood clotting. The condition can lead to repeated and sometimes life-threatening episodes of external and internal bleeding following accidental trauma or medical interventions. The episodes may cause long-term damage, for example to the joints, and may be fatal if they occur in the brain. The deficient blood clotting is caused by the lack of functional human Factor IX, or hFIX, a blood clotting factor, as a result of mutations in the gene responsible for encoding this essential protein. The presence of hFIX at greater than 1% of normal levels has a therapeutic effect in promoting clotting. The current standard treatment is prophylactic protein replacement therapy, in which frequent intravenous administrations of recombinant Factor IX (often 2-3 times per week) are

required to stop or prevent bleeding. Protein replacement therapy is costly (\$150,000-200,000 per patient per year) and burdensome, and does not completely prevent bleeding.

The total Hemophilia B patient population in the European Union and the United States is estimated at approximately 25,000, according to the World Federation of Hemophilia 2010 Report on the Annual Global Survey. About 40% of individuals with the disease have a severe disorder, characterized by functional factor IX levels that are less than 1% of normal, whereas moderately severe Hemophiliacs (about 30% of the Hemophiliac population) have 1%-5% of normal and those with the mild phenotype (the remaining 30%) have between 5% and 40% of normal factor IX levels (www.orpha.net). Based on these estimates Licensee believes that approximately 70-85% of the worldwide patient population would be eligible for treatment with gene therapy. Licensee believes that the treatment would not be appropriate for those patients with very mild disease phenotype.

1.1.2 Overview of AMT-060 Program

The goal of our AMT-060 program is to restore blood clotting on a long-term basis through the introduction of the functional gene for hFIX into the patient's liver cells. **Licensee** is currently in the process of finalizing pivotal (GLP) safety and toxicology studies and preparing to conduct a Phase I trial.

- 1.1.3 Preclinical Development
- Product Profile
 - 1.1.4 *AMT-060 is designed to be delivered systemically through a peripheral vein in a single administration.*

The use of recombinant adeno-associate vectors (rAAV) of serotype 5 (rAAV5) for targeted gene delivery to the liver was pioneered by St. Jude Children's Research Hospital (SJCRH) where for pre-clinical experiments the hFIX expression cassette was packaged into AAV5 capsids in HEK-293T mammalian cells. HEK-293 produced AAV5-hFIX is not suitable for further development because as a production system it is not amenable to large-scale production. To allow up scaling, the expression cassette has now been transferred into uniQure's proprietary baculovirus expression vector system (BEVS) that can be adapted to a GMP setting. The resulting vector produced using the baculovirus expression system is termed AAV5-hFIXco or AMT-060. Licensee also holds a license from SJCRH to the gene cassette used in the currently ongoing Phase I/II AAV 2/8-LP1-hFIXco trial.

AMT-060, rAAV5-hFIXco, is a recombinant adeno-associated vector of serotype 5, consisting of:

· Inverted terminal regions (or ITRs) of the adeno-associated serotype 2

- · A human codon optimized FIX gene (or hFIXco) as the therapeutic gene
- The liver specific promoter, LP1, derived from the human apolipoprotein hepatic control region and the human alpha-1-antitrypsin (or hAAT) promoter

Virus serotype selection

The hFIXco expression cassette and rAAV5 or AAV8 vectors have been extensively studied in mice and non-human primate. Both vectors have been shown to have similar tropism to (preference to transduce) the liver (Nathwani et al., 2007) and AAV5-hFIXco was shown to mediate expression of significant levels of human factor IX in non-human primates (NHP) during a monitoring period of more than 5 years (Nathwani et al., 2011). In this study none of the animals presented elevated liver enzymes levels or other signs of toxicity during the whole observation period. Liver examination by MRI scanning did not reveal any abnormalities in any of the animals.

These pre-clinical data suggest that i.v. administration of the AAV5-hFIXco vector is able to mediate a similar level of human factor IX as presented for AAV8-hFIXco, and such administration is not associated with safety concerns or immunogenicity against the human factor IX.

Pre-clinical Proof of Concept

Pre-clinical PoC studies have been carried out in wild type mice, non-human primates (NHP) and are currently being completed in transgenic Hemophilia B mice. In wild type mice (C57Bl/6) intravenous administration of AMT-060 mice resulted in dose-dependent levels of (human) factor IX levels in murine plasma as determined by ELISA. Human factor IX levels amounted up to 11% of those in normal human plasma 4 weeks after infusion of $5x10^{12}$ gc/kg, demonstrating that AAV5-hFIXco produced in the BEVS is biologically active.

In Rhesus monkeys dosed with AMT-060 ($5x10^{12}$ gc/kg) by intravenous infusion, human FIX levels peaked to 7%-16% of normal human levels one week after infusion, and stabilized to 5-10% of normal human levels 4 weeks after infusion until sacrifice (12 weeks after dosing). These kinetics are in accordance with those observed in previous studies (Nathwani et al., 2007; Jiang et al., 2006), indicating that i.v. administration of AAV5-hFIXco produced in BEVS results in a level of factor IX in plasma that is similar to that produced using AAV5-hFIXco produced in HEK293 cells. Post mortem, (RT)-QPCR demonstrated homogeneous vector DNA delivery and transgene expression in the liver. No signs of adverse reactions were observed. Infusion was associated with slight and transient effects in plasma chemistry shortly after dosing, such as a brief increase of liver enzyme activity levels, consistent with infusion of a viral protein. Necropsy revealed no significant macroscopic or microscopic abnormalities.

Preliminary data in Hemophilia B mice indicate that treatment with AMT-060 induces normalization of FIX levels as well as clotting time.

Non-clinical safety & toxicology studies

The following table presents a summary of the AMT-060 non-clinical safety and toxicology studies that are being conducted to support the clinical development program.

Parameter to be assessed	Study performed	Status
Pharmacokinetics	1) GLP biodistribution in C57Bl/6 mice (180 days) with validated QPCR	Ongoing
	method.	
	2) Biodistribution data in Rhesus macaques (supportive)	
Toxicity	1) GLP toxicity study in Cynomolgus monkeys (180 days)	Ongoing
	2) GLP toxicity study in C57Bl/6 mice (180 days)	
	3) Liver pathology in Rhesus macaques (supportive)	
Off-target expression	Included in the GLP toxicity study in monkey and mouse	Ongoing
Shedding pattern	Partly included in the mouse GLP toxicity study.	Ongoing
	Partly included in the Rhesus macaques study.	
Persistence in semen and risk of	1) Mouse Germline transmission study in C57B1/6 mice	Ongoing
germline transmission	2) QPCR of the testis in the Rhesus macaques at 90 days (non-GLP).	
Carcinogenicity	Analyze tissues from the Rhesus studies using LAM-PCR	Ongoing
Juvenile toxicity	Ethical approval obtained and study is being planned (to support PIP plans)	Ongoing

1.1.5 Summary of AMT-060 Preclinical Development Program

AAV5-hFIXco shows similar liver tropism to AAV8-hFIXco and results in significant and long lasting increase in FIX expression.

• Single intravenous administration of AMT-060 into wild type mice and Rhesus macaques results in significant and long lasting hFIX levels with no noticeable adverse events and no macroscopic or microscopic findings.

• GLP safety and toxicology studies are expected to be completed in December 2013.

- 1.1.6 Clinical Development Program
- 1.1.7 The key regulatory and clinical development milestones for AMT-060 include the following:
- EMA Orphan Drug Designation:

Nov 2011

•	FDA Orphan Drug Designation:		Jan 2012
•	EMA Scientific Advice:		Feb 2012
	EMA Phase I Protocol Advice:		Aug 2012
	GLP Safety & Tox Studies:		2Q2012 to 4Q2013
Expected n	hilestones		
	IMPD submission:		2Q2014
	Phase I start:		3Q2014
	Phase II/III start:	3Q2016	
	MAA/ NDA submission:		2Q2018
	Phase I trial		

The Phase I study will be a multicenter, open label, prospective, interventional, single dose, dose-escalation clinical trial to investigate the safety and tolerability of AAV5-hFIXco (AMT-060) in patients with severe Hemophilia B.

The primary objective is to assess the safety of systemic administration and determine the maximum tolerated doses (MTD). Secondary objectives include:

- · To estimate the appropriate dose required to achieve stable expression of hFIX at or above 3% of normal
- · To evaluate kinetics (dose-related duration and magnitude) of expression
- · To assess the immune response to hFIX transgene product
- · To assess the immune response to the AAV5 capsid proteins
- · To assess viral shedding in various body fluids (including semen)
- · To assess the occurrence of FIX inhibitors
- · To evaluate coagulation parameters
- To assess need for FIX concomitant treatment

Twelve male adults patients (\geq 18 year old to \leq 35 year old) with genetically confirmed Hemophilia B and phenotypically defined as having severe disease (\leq 1% of normal plasma FIX levels) are expected to be enrolled. Initial patient follow-up will last for 12 months as part of the Phase I trial.

Future Clinical Development

1.1.8 It is envisaged that the Phase II/III will be a confirmatory trial where the study population and the outcomes (efficacy endpoints — clinical and biochemical) will be based on those for the Phase I. **Licensee** will also consider expanding the patient population to moderately severe patients and intend to carry out the study in both Europe and USA.

1.1.9

Summary of AMT-060 Clinical Development Program

- The IMPD is planned to be submitted in 2Q2014
- · Phase I is planned in patients with severe Hemophilia B and is expected to start in 3Q2014

It is the intention that in Phase II/III the patient population will expand to moderately severe Hemophilia B patients

• The Phase II/III program will run in parallel in Europe and USA where MAA and NDA, respectively, are expected in 2Q2017

The Hemophilia B program has been partnered with Chiesi. The co-development agreement has ben shared with NIH.

B) Active Research Projects

1. Hemophilia A

Disease Background: Hemophilia A (HA) is a genetic, X-linked, recessive disorder caused by production of dysfunctional or by production of insufficient amount of factor VIII (FVIII) protein, a key protein involved in the blood coagulation cascade. Hemophilia A patients suffer from spontaneous bleeding in the large joints and soft tissue, and are at risk for intracranial hemorrhage. Recurrent episodes of joint bleeding can lead to crippling arthropathy, particularly in severely affected patients. HA comprises the majority of hemophilia patients (80%), with incidence of ~1:10,000 to 1:50,000 males affecting 400,000 people worldwide.

Numerous mutations in the FVIII gene have been described giving rise to different disease phenotypes. Similarly to Hemophilia B (HB), individuals with less than 1% active factor are classified as having severe hemophilia, those with 1—5% active factor have moderate hemophilia, and those with mild hemophilia have between 5—40% of normal levels of active clotting factor.

Clinical need: HA seems an excellent candidate for gene therapy (GT) as it is a well characterized monogenic disorder. The product of the FVIII gene is a plasma protein which is normally secreted by hepatocytes and endothelial cells but can also be expressed in other cell types, e.g., adipocytes, mycoytes or fibroblasts. Furthermore, only modest increase >1% can markedly reduce spontaneous bleedings. The effects of gene therapy can be readily monitored by changes in phenotype and by obtaining peripheral blood to measure FVIII antigen levels and clotting factor activity. Currently, treatment for HA consists of infusion of either plasma-derived or rFVIII protein for bleeding episodes. Although, prophylactic infusion of FVIII concentrates is generally effective in alleviating bleeding episodes and subsequent joint disease, the short half-life of FVIII (~12 hours) and the high cost of purified FVIII products make life-long prophylactic treatment demanding for patients and costly.

Feasibility

Gene: The gene of factor VIII is located on the long arm of the X chromosome. It spans over 180 kb, and as such is one of the largest genes known. It comprises of 26 exons, which encode a polypeptide chain of 2351 amino acids including a signal peptide of 19 and a mature protein of 2332 amino acids. It is a secreted protein. Its primary structure, deduced from the cloned factor VIII cDNA, includes discrete domain structure: A1-a1-A2-a2-B-a3-A3-C1-C26-8. The B domain is unique in that it exhibits no significant homology with any other known protein and can be deleted with the resulting recombinant protein displaying essentially normal survival in circulation and able to correct the bleeding tendency in HA patients.

Vector optimization: A rAAV5 containing HLP-hFVIIIco (promoter HLP; codon optimized hFVIII with partial B-domain deletion) has been generated in-house where the preserved B-domain consists of 225 N-terminal amino acids containing 6N-glycosilation sites. This variant has been previously shown to increase secretion of FVIII as

compared to wild type or to FVIII with complete B-domain deletion and in-house work with HLP-hFVIII has shown that it produces active FVIII protein *in vitro and in vivo*.

This FVIII expression cassette size is however \sim 5.6 kbp, which exceeds the AAV packaging limit (4,7-4,9 kbp). In-house molecular analysis studies of the encapsidation products showed that the 5.6 kbp FVIII expression cassette is not entirely encapsidated in the AAV particle. Instead + and – DNA strands of the encapsidated molecules revealed missing 5' ends. This is consistent with previously reported unidirectional (starting at 3' end) packaging mechanism operating according to "head-full principia" with 4.7-4,9 kbp limit. **Licensee** hypothesizes that the correct template for production of FVIII was assembled in the target cell based on complementation of + and – DNA strains each of which delivering the 5' missing end. This is to be expected since + and – strain complementation is responsible for normal rAAV episome formation. **Licensee** proposes therefore to develop a product that consist of incomplete + and – DNA strains, which are assembled into complete expression cassette upon episome formation.

A proof of concept study has been initiated involving a number of FVIII construct and including full FVIII codon optimized gene. The study aims to characterize the viral DNA, formation of episomes upon delivery of the expression cassette to the nucleus, resulting mRNA and FVIII protein. The potency of the vector is currently being investigated in a number of animal models.

It is our aim to develop this product to clinical stage Phase I by the end of 2015. Duration of clinical development and further timelines have not been defined.

Development overview to IMPD:

					11.11											1	Dura	ation	n (m	ont	hs)															
		1	2	3	4	5	6	7	8	9 1	0 1	12	2 13	8 14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Res.	Vector optimisation	10-1																																		
(with VP unit & BloAD)	Baculovirus production																																			
3	Res. batch production																																_			
	In vitro/ in vivo testing																																			
	Remake of baculovirus (P2)																125																			
PD	MSV, WSV & P5 generation																																			
	GLP tox. Batch production																																	-		
AD	GLP Tox batch analysis																																			
NC	Pilot tox studies																																			
	Small rodent GLP tox studies																																			
	NHP GLP tox studies																													T						
PD/ MF (QC & QA)	Process transfer to GLP																		1							4	1.1						-	1		
	Phase I batch production																																			
RA	IMPD																													1				1		

Completion of vector optimization work will provide the first milestone (Go/No Go) for the project.

Safety Assessment: The disease and gene therapy approach are similar (or equivalent) to Hemophilia B where no major safety concerns have been described.

2. Cirrhosis

Disease Background: Liver cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (resulting from regeneration of damaged tissue), leading to loss of liver function. The four leading causes of cirrhosis and primary liver cancer in Europe include harmful alcohol consumption, viral hepatitis B, viral hepatitis C and metabolic syndromes related to overweight and obesity. The European Association for the Study of the Liver in its 2013 report reported that approximately 29 million people in the European Union suffer from a chronic liver condition and that the incidence and prevalence of two conditions, cirrhosis and primary liver cancer, are key to understanding the burden of liver disease. Both conditions represent the end-stage of liver pathology and thus are indicative of the associated mortality.

The hypothesis behind this project is that liver cirrhosis is a state of IGF-I insufficiency and low expression of IGF-I locally in the liver will revert and/ or prevent further exacerbation of cirrhosis. A confidentiality agreement concerning this project was signed between DIGNA/ CIMA and uniQure in October 2012.

Pre-clinical evidence to support this hypothesis includes the following:

- Proof of Mechanism: SV40-IGF-I administration in rat cirrhotic liver models resulted in increased mRNA and protein levels of IGF and IGF-BP3 compared to control animals in the hepatocytes and levels remained constant for up to 6 months (Sobrevals et al., 2010).
- Proof of Principle: SV40-IGF-I mediated expression in rat cirrhotic liver models, induced fibrolysis through upreguation of MMPs and downregulation of TIMP-1/-2, reduced expression of pro-fiborgenic factors (TGFb, amphilregulin, PDGF, CTGF, VEGF), induced antifibrogenic and cytoprotective factors (HGF), promoted hepatocyte differentiation through upregulation of HNF4a and downregulation of WT-1 (Sobrevals et al., 2010).

Treatment with recombinant IGF-I protein resulted in improved hepatic function, decreased oxidative stress/ damage, improved mitochondrial function and decreased fibrosis (Castillo-Cortazar et al., 2000; García-Fernández et al., 2005; Lorenzo-Zuniga et al., 2006).

 Proof of Concept: SV40-IGF-I-mediated expression in rat cirrhotic liver reversed fibrosis by decreasing expression of collagen I & IV and deactivation of HSC, and improved liver function through normalisation of AST, ALP, bilirubin and albumin (Sobrevals et al., 2010).

Clinical evidence to support disease linkage includes the following:

- In patients suffering from liver cirrhosis circulating IGF-I levels (or IGF-BP3) correlate with disease severity scores; Child-Pugh and MELD (Kratzsch et al., 2005; Khoshnood et al., 2013).
- A short course (for 4 months) of IGF-I recombinant therapy treatment increased the levels of albumin and tended to improve energy metabolism (surrogates for liver function) & the levels of serum albumin positively correlated with IGF-I/IGF-I BP3 ratio (Conchillo et al., 2005).

Clinical need: Transplantation is the only curative option for the disease and contraindications to transplantation include, a) co-morbidities (e.g., TB), b) over 65 years of age, c) coronary artery disease and d) tumours in previous 5 years.

The initial target population for IGF-I gene therapy for liver cirrhosis could/ would be those cirrhotic patients with IGF-I insufficiency (i.e., 50% of all cirrhotic patients), possibly patients with Child-Pugh A and/ or B score and with IGF-I levels below normal values. An ODD application for this specific population may be considered. The table below indicates the Child-Pugh scoring scheme for liver disease prognosis.

Points	Class	One Year Survival	Two Year Survial
5-6	A	100%	85%
7-9	В	81%	57%
10-15	С	45%	35%

Feasibility:

Gene: The IGF1 gene is located on chromosome 12 and spans 7.3 kb encoding a 70 amino acid residue protein. It contains 6 exons, 4 of which are alternatively spliced depending on tissue type and hormonal environment. The IGF1 coding region is flanked by sequences encoding an amino-terminal peptide of at least 25 residues and a

carboxyl-terminal peptide of 35 amino acids which indicates that IGF1 is synthesized as a precursor protein that undergoes proteolytic processing at both ends before being secreted.

Vector optimization: The IGF-1 rat version is available with CIMA and was used for proof of concept studies. Human IGF-I vectors are being developed in-house as part of work done by the Emerging Technologies Research Group on regulated gene expression systems.

Animal models: A rat model is available with CIMA and has been used for proof of concept studies. A number of other small animal models have been described (Liu et al., 2013).

Biomarkers: Circulating IGF-I (and other related proteins) can be monitored using commercially available methodology. However the relevance of this to liver (local) levels of IGF-I and whether GT can deliver sufficient amounts of IGF-I that that can be readily detectable in the circulation need to be established.

Liver function and signs of cirrhosis can be monitored following well established standard procedures (e.g., liver enzymes, markers of fibrosis etc.).

The PoC obtained at CIMA will have to be repeated with uniQure's AAV5-IGF1 vector. Licensee is at the initial stages of research aiming to initiate a Phase I clinical trial by the end of 2016.

Development overview to IMPD:

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		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Res.	Vector generation		1100											-										_						_			-				
(with VP unit & BioAD)	Baculovirus production																																				
	Res. batch production																																			Ľ.,	
	In vitro/ in vivo testing					_																															
	Remake of baculovirus (P2)							_																													
PD	MSV, WSV & P5 generation										-				1																		_				
	GLP tox. Batch production																																				
AD	GLP Tox batch analysis																																				
NC	Pilot tox studies																																				
	Small rodent GLP tox studies																						-		1									-			
	NRP GLP tox studies			-																																	
PD/ MF (QC & QA)	Process transfer to GLP																																				
	Phase I batch production																																				
RA	IMPD																								1				13								

The GLP safety and toxicology studies will provide the first milestone (Go/No Go) for the project.

Safety Assessment: Safety studies in rat disease models (8 months) and wild type rats (8 weeks) showed no signs of toxicity due to treatment with SV40-IGF-I (Sobrevals et al., 2010).

Potential toxicity concerns include tumor formation and interference with insulin/ glucose metabolism albeit both issues are unlikely as the aim of this approach would be to upregulate levels of IGF-I where they are already below normal rather than to achieve supra-physiological levels. In addition, gene

therapy vectors are likely to induce lower level of localized expression without substantial increase in serum IGF-I levels. Regarding potential for tumorigenesis, IGF-I therapy is thought to favor hepatocellular differentiation, i.e., opposes carcinogenesis, and studies have shown that sharp decrease in IGF-I in cirrhotic liver may contribute to hepatocellular carcinoma (HCC). In addition it is believed that it is IGF-II that is the key player in HCC. Furthermore, patients with existing tumor nodules in their liver could/ should be excluded from trials.

[NOTE: Hepatocellular carcinoma occurs at a rate of 1% to 4% per year after cirrhosis is established and cirrhosis underlies HCC in approximately 80%-90% of cases worldwide (Giovanna Fattovich et al., 2004), i.e., the vast majority of cirrhotic patients do not develop HCC or at least they do not live live long enough to develop it]

3. Hyperoxaluria

Disease Background: Primary hyperoxaluria type I (PH1) is a rare, autosomal recessive inherited metabolic disorder characterized by a deficiency of the hepatic enzyme alanine-glyoxylate aminotransferase (AGXT), which produces a marked increase in endogenous oxalate synthesis by the liver. Oxalate is a metabolic end product in humans and excess oxalate provokes hyperoxaluria, causing progressive urolithiasis, nephrocalcinosis and chronic renal failure, ultimately leading to end-stage renal failure (ESRF) and death if untreated.

It is the most common and severe variant among a spectrum of metabolic disorders resulting in hyperoxaluria. The disease has an estimated prevalence ranging from 1 to 3 per 1 million individuals and an estimated incidence of 1-9:100,000 live births per year in Europe. However, higher rates are reported in historically isolated populations, like the Canary Islands. PH1 accounts for <1% of pediatric ESRF in developed countries.

A pre-clinical proof of concept study has already been conducted in collaboration with Eduardo Salido (University Hospital of Canary Islands) using AGXT knockout mice demonstrating that in the GT treated animals oxalurea reduced to normal levels with restoration of liver enzyme levels in the absence of any hepatotoxicity or immune reactions.

Clinical need: Currently, most of the therapeutic options are diet-mediated to reduce the amount of glyoxylate intake and maximize the intake of vitamin B6. The most effective treatment for PH1 is pre-emptive liver transplantation, alone or liver combined with kidney transplantation in ESRF. There is therefore a clear need for alternative or new treatments options.

Feasibility:

Gene: the AGXT gene maps onto chromosome 2q36-q37, has a 10 kb coding sequence and contains 11 exons generating a 392-residue protein.

Vector optimization: Eight constructs different containing codon optimized AGXT genes have already been generated in-house and are currently being characterized.

Animal models: Small animal models already exist and have been used for pre-clinical proof of concept studies.

Biomarkers: Measurements of oxalate are part of routine clinical practice for the disease setting and monitoring of kidney changes can also be done using standard techniques.

After a phase of further vector optimization it is our aim to develop this product for a first Phase I clinical study by mid 2016. Further development timelines have not been defined.

Development overview to IMPD:

		100												t	Durat	tion	(mo	nths)						_						- 3
	V6. (0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Res.	Baculovirus production					Τ		1																							
(with VP unit & BioAD)	Res. batch production																														
	In vitro/ in vivo testing																														
	Remake of baculovirus (P2)																														
PD	MSV, WSV & P5 generation																														
	GLP tox. Batch production												-		1	-															
AD	GLP Tox batch analysis																														
NC	Pilot tox studies										-	1																			
	Small rodent GLP tox studies					L																									
	NHP GLP tox studies																														
PD/ MF (QC & QA)	Process transfer to GLP																													-	
	Phase I batch production																														
RA	IMPD																														

The GLP safety and toxicology studies will provide the first milestone (Go/No Go) for the project.

Safety Assessment: At this stage is not possible to make any inferences in relation to potential safety concerns.

C) Exploratory Research Projects

The projects listed under this category in Table 1 above are not in active research yet, but are likely targets for our platform technology and are being assessed on feasibility before starting active bench work.

Central Nervous System Programs

A) Development Programs

1. AMT-110 for Sanfilippo B

1.1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis type III (MPSIII), is a rare lysosomal storage disorder (LSD) that occurs when enzymes needed to break down the heparan sulfate sugar chain are missing or are defective. Sanfilippo B is one of the four types of MPSIII that results in serious brain degeneration in children, and is generally lethal. The deficient enzyme responsible for the disease is alpha-N-acetylglucosaminidase (NaGlu). The clinical manifestations are mainly neurological, with early symptoms observed during the first five years of age, leading to a progressive deterioration of cognitive abilities. Affected children require specific care after age seven and progressively develop profound mental retardation with reduced somatic manifestations. Death frequently occurs at the median age of 15. No treatment is currently available.

Birth prevalences of 0.28—4.1 per 100, 000 have been reported (Valstar et al., 2008). More recently, He'ron et al. (2010) estimated the mean annual incidence for Sanfilippo B in France at 0.15 per 100,000 births.

1.1.2 Overview of AMT-110

The goal of our AMT-110 program is to provide a gene therapy for Sanfilippo B syndrome through the introduction of a functional NaGlu gene into the patients' brain cells.

This project is being pursued together with the Pasteur Institute (Paris) whereby uniQure is responsible for developing the manufacturing process and producing clinical grade material and the Pasteur Institute for conducting the clinical trials.

- 1.1.3 Preclinical Development
- Product Profile

AMT-110 is designed to be delivered via intracranial administration.

AMT-110 or rAAV5-hNaGlu, is a recombinant adeno-associated vector of serotype 5, consisting of:

- Inverted terminal regions or ITRs of the adeno-associated serotype 2
- A human α-N-acetylglucosaminidase, or hNaGlu, gene the therapeutic gene
- The mouse phosphoglycerate kinase-1 promoter (muPGK)
 - · Pre-clinical Proof of Concept

Preclinical PoC studies were conducted in mouse and dog disease models at the Pasteur Institute. These studies showed that mice with MSPIIIB a single AAV5-NaGlu intracranial injection

resulted in reversion of storage lesions throughout the brain and prevented loss of Purkinje cells. Furthermore, it improved animal behavior and corrected pathological featured of the disease including, neuro-inflammation, axonal transport, synaptic vesicle content and the autophagy defect.

In MSPIIIB dogs treatment (four simultaneous injections) with AAV5-hNaGlu was well tolerated, vector particles were broadly distributed and the therapeutic enzyme was delivered to the entire brain leading to improvement in MPSIIIB-induced histological lesions and normalization of glycosaminoglycan and ganglioside levels. These studies also confirmed that the combination of gene therapy with efficient immunosuppression was required for treatment efficacy.

• Non-clinical safety & toxicology studies

The following table presents a summary of the AMT-10 non-clinical safety and toxicology studies that have been conducted to support the clinical development program.

Parameter to be assessed	Study performed	Results
Pharmacokinetics	1) GLP biodistribution in Sprague-Dawley rats	In in Sprague-Dawley rats:
	with or without immunosuppression (180 days)	• Constant high number of genome copies present in the brain with no vector in the
	2) GLP biodistribution in Dogs with immunosuppression (90 days)	blood at 3 months.
		 No difference between immunosuppressed and non-immuno-suppressed animals.
		In dogs
		 Organs negative for vector DNA (< LOQ) were heart, lung, kidney and testis whereas positive organs (> LOQ) included spleen, liver and cervical spinal cord.
Toxicity	GLP toxicity study in Sprague-Dawley rats (180 days)	• No specific toxicity
		 Only injection traces in the brain at some injection sites

(French Authorities endorsed the use of a sing species for safety and toxicology studies)	 No effect on body weight, growth, food consumption, behaviour No decedents, no inflammation No histopathological findings NOAEL: 3.4 x 10¹¹/animal
Persistence in semen and risk of	Based on pilot dog preliminary data where no vector DNA was found in the
germline transmission	gonads, French Authorities endorsed the proposal that no germline transmission studies were necessary.
1.1.4 Summary of AMT-110 Preclinical D	evelopment Program
• In animal models of Sanfilippo B, treatment with AAV5-hNaGlu ameliorated pathophysic	ological signs and symptoms of the disease.
• AMT-110 administered into the striatum of non-immunosuppressed rats and immunosup vector DNA in the brain and caused no mortality and no signs of toxicity.	pressed rats and dogs produced long lasting presence of
1.1.5	
1.1.6 Clinical Development Program	
1.1.7 The key regulatory and clinical development milestones for AMT-110 include	the following,
• 1 st Scientific Advice with French Regulatory Authorities	March 2012
• 2 nd Scientific Advice with French Regulatory Authorities	March 2012
· IMPD Submission	April 2013
· IMPD Approval	3Q13
· Phase I start	0 + 1 - 2012
	October 2013
Expected Milestones	October 2013

The Phase I/II study is a single center, open label, prospective, interventional, single dose of AAV5-hFIXco (AMT-060) trial in children with Sanfilippo type B syndrome. Administration will be performed into the brain parenchyma and cerebellum at 8 image-guided tracks, with 2 deposits per tracks, in a single neurosurgical session. Each patient will receive 960 μ L of vector suspension as 16 simultaneous vector deposit each containing 2.4 10¹¹ gc (4 10¹² gc in total). Patients will receive immunosuppression starting 10 days prior to treatment.

2018

The primary objective of the study is to evaluate the clinical, radiological and biological safety of the treatment. The secondary objective is to collect samples and data to define exploratory tests that could become evaluation criteria for further clinical efficacy studies (Brain MRI; neurological tests and biological markers).

The study will be conducted at the Bicêtre Hospital which is part of the University Hospitals of South Paris and is expected to enroll a total of 4 children during an 8 to 12 months inclusion period. The duration of follow-up for each patient is one year. The first patient was dosed in October 2013.

Future Clinical Development

Registration

Licensee plans to complete the Phase I and start a Phase II/III trial in multiple sites worldwide. Following initiation of this trial one of the options on how to proceed would be applying for approval for compassionate use to treat on a named patient basis. This can be well justified based on the size of the indication and lethality of the condition.

1.1.8 Summary of AMT-110 Clinical Development Program

- The IMPD was submitted in April 2013
- Phase I was started in October 2013

B) Active Research Projects

1. Huntington's Disease

Disease background: Huntington's Disease (HD) is a neurodegenerative genetic disorder that affects motor control and leads to cognitive decline and dementia. It typically becomes noticeable in middle age, but can begin at any age from infancy to old age. HD has a prevalence of around 1 affected individual in 100,000.

The mutated form of the protein huntingtin causes cellular dysfunction and death in a number of CNS sites but is most noticeable in the striatum and cortex. The mutation is caused by CAG repeats in the DNA of patients. The earliest features of HD are involuntary movements and irritability and a loss of executive function. This progresses over time and in the more advanced stages, the patient is demented and bed-bound. The disease is currently incurable with patients dying about 20-25 years after it begins.

Clinical need: The clinical need for these patients is high as there is no cure for the disease.

Feasibility

As the CAG repeats in the Huntingtin gene are the cause of the disease, downregulation of the expression of the CAG repeats is an option. Also rescuing the neurons from degeneration using GDNF is an option. Both options are currently under investigation. Replacing the gene is not an option as this is far too large to fit into an AAV vector.

Several transgenic mice models exist. Severity and time of onset are based on the number of CAG repeats in the model. Mostly used are the R6/1 and R6/2 transgenic models.

Preclinical work: Proof of concept using GDNF has been established in one laboratory. Licensee is currently trying to establish this with our own vector in the laboratory of Roger Barker.

Proof of concept with siRNA has been established in mice models and Licensee is in the process of implementing this into our studies.

Development overview to IMPD:

		1	2	3		4	5	6	7	8	9	10	11	12	1	5 10	5 1	7 11	8 1	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Res.	In vitro/ in vivo testing (PoC)																		T																-	
(with VP unit & BioAD)	Remake of baculovirus (P2)				Г												1		T					5			-						1	-	1	
PD	MSV, WSV & P5 generation						Τ								Γ																					
	GLP tox. Batch production				Г		Τ							Г	Г				T					1										2		
AD	GLP Tox batch analysis						Τ												Т															1		
NC	Pilot tox studies				Г	T	Т						Г	Г	Г	T	T		Т														Ĭ.	1		
	Small rodent GLP tox studies				Г		Τ								Г									3	22	12			131	22				8	8	
	NHP GLP tox studies				Γ		Τ								Γ				T)		
PD/ MF (QC & QA)	Process transfer to GLP														Γ									1	100	7										
	Phase I batch production				Γ	1	Τ								Γ				Τ						1					8						
RA	IMPD																																			

The proof of concept studies (in vivo/ in vitro work) will provide the first milestone (Go/No Go) for the project.

With regards to the siRNA approach to HD, vector generation & optimization will require an additional 9 months prior to any other activity. Then a similar development path to what is shown above will need to be followed.

It is Licensee's aim upon a successful PoC to develop this product further to a Phase I clinical investigation which should start mid 2016.

Collaborators: Licensee is working together with Roger Barker (Cambridge University) on the use of GDNF to rescue neurons in Huntington models, based on a EUREKA grant. **Licensee** is also working together with Nicole Deglon (Lausanne University), Anna Skorupska (Lublin University) and Sebastian Kuegler (Gottingen University) in a Eurostars grant setting. Competition comes from siRNA companies.

Safety concerns: Potential safety concerns could be the complete downregulation of the Huntingtin gene, even though not fully supported by the Eurostars team. The use of GDNF could lead to side effects, such as weight loss.

IP: For GDNF, Licensee has a license from Amgen. For the siRNA work Licensee has a non-exclusive license from Benitec.

2. Multiple System Atrophy

Disease Background: Multiple System Atrophy (MSA) is a sporadic neurodegenerative disease that is characterized by the presence of glial inclusion bodies, which stain positive for a synuclein. The clinical picture is that of parkinsonism, autonomic failure, cerebellar ataxia and pyramidal signs in differing combinations. Approximately 80% of patients present with predominantly parkinsonian features (MSA-P) manifesting in rapidly deteriorating akinesia, rigidity, postural instability and high pitched dysarthria. Most such patients do not exhibit the classic resting tremor of Parkinson's disease and virtually all develop frank dysautonomia in the course of the illness. The cause of the disease is not known.

Clinical need: Although a minority of patients may achieve modest benefit from dopaminergic therapy, there is no satisfactory treatment for the parkinsonian disabilities of MSA-P. Additionally, deep brain stimulation of the subthalamic nucleus has been of little or no value. Within 5 years of disease onset patients die so the clinical need is high for these patients.

Feasibility:

MSA is not a single monogenic disease, but may be treated with a single neuroprotective protein. In this case, this could be GDNF. Some transgenic animal models exist, all overexpressing the alpha-synuclein protein. The rationale to use GDNF (besides its general neuroprotective effect on neurons) is that both in patients and the transgenic mouse model, GDNF expression is downregulated. Introduction of an elevated level of GDNF may

serve as the treatment. Read out parameters for the disease progression are all related to those of Parkinson's Disease. PoC has not yet been established, but is under investigation in the mouse model.

Development overview to IMPD: a

		1	2	3	4	5	6	7	8	3	9 1	0 1	1	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Res.	In vitro/ in vivo testing (PoC)										T																					
(with VP unit & BioAD)	Remake of baculovirus (P2)								1.1								1										1					1
PD	MSV, WSV & P5 generation																	1														- 33
	GLP tox. Batch production						÷.																									
AD	GLP Tox batch analysis									Г	Т		Τ																			
NC	Pilot tox studies													- 2										-								
	Small rodent GLP tox studies									Γ										9-1					-							
	NHP GLP tox studies									Γ			Τ																			
PD/ MF (QC & QA)	Process transfer to GLP																															
	Phase I batch production				с. — Т		1			Т	Т											1										
RA	IMPD																							1					1.1			

The proof of concept studies (*in vivo/ in vitro* work) will provide the first milestone (Go/No Go) for the project. It is our aim upon a successful PoC to develop this product further to a Phase I clinical investigation which should start mid 2016.

Collaborators: Licensee is working together with Erwan Bezard (University of Bordeaux) and Olivier Rascol (University of Toulouse) who are together running the French reference center for MSA.

Safety Assessment: The use of GDNF could lead to side effects, such as weight loss. The exact mechanism through which the treatments would have its effect is not clear yet.

3. Hearing loss

Disease background: Hearing loss is a serious clinical problem. Underlying mechanisms for the loss of neurons in the cochlea can vary from ischemia, mechanical stress to toxic insults. The actual numbers of patients is not easy to define, but it could be rather large. When age-related hearing loss is also taken into account, this is no longer an orphan indication.

Clinical need: Patients with hearing loss could be helped with cochlear implants. However, progressive neurodegeneration is not stopped by that. There is high clinical need as there is no cure for the disease.

Feasibility:

Neuron function and survival is dependent on a delicate balance of neurotrophins. Following trauma or toxic insult to neurons, they may slowly die. To reverse this state of degeneration, it could be beneficial to supply the neurons with a neurotrophin such as GDNF. This neurotrophin has been shown to be able to rescue neurons from degeneration in several models, including those of the substantia nigra and for instance motorneurons in the spinal cord after trauma.

Animal models are available and include for instance use of Kanamycin in cats, mice or guinea pigs. Also chemotherapeutic agents from the class of statins are used.

Preclinical work: Proof of concept using recombinant brain-derived neurotrophic factor (BDNF) and/or GDNF has been established. Licensee is currently trying to establish this with our own vector in the laboratory of Patricia Leake.

Cochlea of mice can be transduced to express a recombinant transgene.

Development overview to IMPD:

		1	2	3	4	5	6	7	8	9	10	11	12	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	3	5 30	6
Res.	In vitro/ in vivo testing (PoC)	22		100		-		1		1000	1	100	1																							
(with VP unit & BioAD)	Remake of baculovirus (P2)	1						20					1		feel.	3																1	2			
PD	MSV, WSV & P5 generation																																			
	GLP tox. Batch production							1																								1				
AD	GLP Tox batch analysis																																			
NC	Pilot tox studies	1													1	100				1												1				Ī
	Small rodent GLP tox studies				1	1																		111				150				2	1			
	NHP GLP tox studies							- 1																111				10								ĺ
PD/ MF (QC & QA)	Process transfer to GLP				1			- 3													- 3		6	191	1								2			
	Phase I batch production																																			
RA	IMPD							- 1																									-			

The proof of concept studies (in vivo/ in vitro work) will provide the first milestone (Go/No Go) for the project.

This new project has just been initiated upon a successful PoC it is our aim to develop this product further to a Phase I clinical trial, which should start by the end 2016.

Collaborators: Licensee is working together with Patricia Leake (University College of San Francisco) on the use of GDNF to rescue neurons in mouse and cat models. She is the investigator who developed the cochlear implant. This could also be included in the experimental plan.

Safety concerns: The use of GDNF could lead to side effects. Weight loss is not expected, but as the GDNF also has a neurotrophic effect, nerve fibers could sprout in an aberrant way possibly leading to incorrect connections.

IP: For GDNF, Licensee has a license from Amgen; the program as a whole is under investigation.

C) Exploratory Research Projects

The projects listed under this category in Table 1 above are not in active research yet, but are likely targets for our platform technology and are being assessed on feasibility before starting active bench work.