Deutsche
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Herrn
Dr. Mathias Konstandin
Universitätsklinikum Heidelberg
Medizinische Klinik, Innere Medizin III
Kardiologie, Angiologie und Pulmologie
Im Neuenheimer Feld 410
69120 Heidelberg

GZ: KO 3900/2-1 AOBJ: 618340 09.02.2015 Sti

Sehr geehrter Herr Dr. Konstandin,

die Deutsche Forschungsgemeinschaft bewilligt Ihnen und Ihrer Hochschule entsprechend Ihrem Antrag, den Sie zum Thema "Einfluß der extrazellulären Matrix auf physiologische Hypertrophie des Herzens" gestellt haben, Mittel bis zur Höhe von Euro für 36 Monate.

Es handelt sich hierbei um eine flexibilisierte Förderung im Sinne der Ziffer 1 der Verwendungsrichtlinien.

Im Einzelnen werden Ihnen für die Module - Basismodul - die folgenden Mittel bewilligt:

	Anz.	Vol.	Dauer	Euro
KO 3900/2-1				
Dr. Mathias Konstandin			**36 Mon.**	
durch DFG finanziert				
Personalmittel				
Postdoktorand/in und Vergleichbare	1	100%	36 Mon.	
nichtwissenschaftliche/r Mitarbeiter/in	1	50%	36 Mon.	
Sachmittel				
Investitionsmittel				
Programmpauschale				

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Dem darüber hinausgehenden Antrag konnte leider nicht entsprochen werden. Die Inanspruchnahme der Bewilligung setzt im Regelfall das Vorhandensein eines Beschäftigungsverhältnisses zwischen dem bzw. der Projektleiter/in und der wissenschaftlichen Einrichtung, an der das Projekt durchgeführt wird, über die gesamte Laufzeit des Projekts voraus; mindestens jedoch das Vorhandensein entsprechender Arbeitsmöglichkeiten.

Die Deutsche Forschungsgemeinschaft bewilligt Personalmittel grundsätzlich in Form von pauschalierten Beträgen. Die Beträge werden von der Geschäftsstelle der Deutschen Forschungsgemeinschaft anhand typisierter Fallgruppen in Verbindung mit den dafür einschlägigen Tarifmerkmalen, der vorgesehenen Arbeitszeit (Vollzeit- oder Teilzeitbeschäftigung) und der Beschäftigungsdauer ermittelt. Die Beträge beruhen auf „Bruttoarbeitgeberkosten". Sie enthalten u. a. die Arbeitgeberanteile zur Sozialversicherung (einschl. Zusatzversorgung) und zu den vermögenswirksamen Leistungen sowie die Jahressonderzahlung (sog. Weihnachtsgeld). Der Bedarf für mögliche Tariferhöhungen oder Steigerung der Sozialversicherungsabgaben während der Projektlaufzeit ist ebenfalls pauschaliert berücksichtigt.

Die tarifrechtliche Einordnung obliegt ausschließlich der Forschungseinrichtung bzw. dem Klinikum als Arbeitgeber.

Es gilt das an Ihrer Einrichtung maßgebliche Tarifrecht.

Sofern das an Ihrer Einrichtung maßgebliche Tarifrecht auf einem Haustarif beruht und sowohl vom TVL als auch vom BAT abweicht, können die bewilligten Mittel für Personal verwendet werden, das Tätigkeiten wahrnimmt, die den Tätigkeitsbeschreibungen der korrespondierenden Vergütungsgruppen des BAT entsprechen.

Die bewilligten Sachmittel dürfen nicht für die sich aus diesem Schreiben ergebenden, ausdrücklich abgelehnten Positionen und - unabhängig davon - auch nicht für die "nicht abrechenbaren Kosten" nach Ziffer 6 der Verwendungsrichtlinien (DFG-Vordruck 2.02 - 04/14) eingesetzt werden.

Bei der Programmpauschale handelt es sich lediglich um eine kalkulatorische Größe auf Basis der bewilligten Personal-, Sach- bzw. Investitionsmittel. Die tatsächliche Höhe der Programmpauschale beträgt 20 % der abrechenbaren direkten Projektausgaben.

Über die Verwendung der Programmpauschale entscheidet Ihre Hochschule, zu den Programmpauschalen siehe auch Ziffer 1.2 der Verwendungsrichtlinien (DFG-Vordruck 2.02 – 04/14).

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Aus der Begutachtung haben sich Hinweise zu dem Projekt ergeben, die Ihnen noch in einem separaten Schreiben mitgeteilt werden.

Bei Fragen zur finanziellen Abwicklung der bewilligten Mittel wenden Sie sich bitte unter Angabe des Geschäftszeichens KO 3900/2-1 und des dazugehörigen Abrechnungsobjektes 618340 an den Bereich Prüfung und Abrechnung, E-Mail FIN2@dfg.de.

Die beigefügten Verwendungsrichtlinien (DFG-Vordruck 2.02 – 04/14) sind Bestandteil dieser Bewilligung.

Ihre Hochschule wird mit einem Schreiben gleichen Datums zum obigen Geschäftszeichen auch über den Umfang der Bewilligung informiert.

Sie werden gebeten, den Vertrauensdozenten Ihrer Hochschule für Angelegenheiten der Deutschen Forschungsgemeinschaft Herrn Professor Dr. Peter Comba, Im Neuenheimer Feld 270, 69120 Heidelberg, von dieser Bewilligung zu unterrichten.

Mit Annahme dieser Bewilligung verpflichten Sie sich, gleich nach Abschluss Ihres Projekts über die Ergebnisse zu berichten (siehe "Leitfaden für Abschlussberichte" in den beigefügten Verwendungsrichtlinien, Ziffer 16), wir haben dafür als Termin vorläufig den 01.04.2018 notiert.
Wenn Sie jedoch einen Fortsetzungsantrag zu diesem Projekt stellen, so fügen Sie bitte nur diesem einen Zwischenbericht bei.

Die zur Bearbeitung Ihres Antrags erforderlichen Daten wurden von der DFG elektronisch gespeichert und verarbeitet. Zu der hier bewilligten Fördermaßnahme werden Adress- und Kommunikationsdaten zur Person (Telefon, Fax, E-Mail, www-Homepage) sowie inhaltserschließende Angaben (z. B. Thema, Zusammenfassung, Schlagwörter, Auslandsbezug) in der Projektdatenbank GEPRIS (vgl.: http://www.dfg.de/gepris/) sowie - in Auszügen (Name, Institution und Ort der Antragsteller) - im Teil "Programme und Projekte" des elektronischen Jahresberichts (http://www.dfg.de/jahresbericht/) veröffentlicht. Wenn Daten anders als in der Ihrem Antrag entnommenen Form angegeben werden sollen oder keine elektronische Publikation erfolgen soll, teilen Sie uns dies bitte innerhalb einer Frist von vier Wochen schriftlich mit.

Die Deutsche Forschungsgemeinschaft wünscht Ihnen für Ihre Arbeit guten Erfolg.

Mit freundlichen Grüßen

Dr. Tobias Grimm

DFG

INVESTIGATOR-SPONSORED STUDY AGREEMENT

This Investigator-Sponsored Study Agreement (this "**Agreement**"), is made on the date of last signature below (the "***Effective Date***"), by and among:

(1) **Alnylam Pharmaceuticals, Inc.**, 300 Third Street, Cambridge MA 02142 ("***Alnylam***"),

(2) **University of Heidelberg,** Department of Cardiology, Im Neuenheimer Feld 410, D69120 Heidelberg, Germany (the "***Institution***"), and

(3) **Professor Arnt V. Kristen, MD** (the "**Sponsor-Principal Investigator**"),

(together, the "***Parties***" or each, individually, a "***Party***").

WHEREAS, the Sponsor-Principal Investigator, an employee of the Institution, has designed and intends to initiate a clinical research study (the "**Study**"), to be sponsored and conducted by Sponsor-Principal Investigator at the Institution, pursuant to the proposal (the "**Proposal**") attached hereto as **Exhibit B**, in accordance with all legal and regulatory requirements;

WHEREAS, the Sponsor-Principal Investigator has submitted the Proposal to Alnylam and requested certain support from Alnylam to facilitate the independent conduct of the Study;

WHEREAS, Alnylam, in response to the Sponsor-Principal Investigator's request, wishes to provide limited support for the Study under the terms and conditions set out in this Agreement; and

NOW THEREFORE, in consideration of the above, and of the mutual covenants and promises contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties further agree as follows:

1. Definitions & Interpretation

1.1. For the purposes of this Agreement, the following words and expressions shall have the following meanings:

"Applicable Laws and Regulations"	means all laws, rules, obligations and recognized industry guidelines concerning, governing or impacting any legal, ethical and/or regulatory requirements, obligations and/or best practices for the conduct of clinical research, including, without limitation, the World Medical Association Declaration of Helsinki, the International Conference on Harmonization (ICH) Guidelines (including those for Good Clinical Practices), and the laws of any relevant Regulatory Authority where the Study is being conducted.
"Disqualified Person"	means any person subject to limitations or any form of enforcement imposed upon clinical investigators or clinical study sites by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) or any Regulatory Authority or other recognized national, multi-national or industry body. For the sake of clarity, a person subject to debarment under the Applicable Laws and Regulations of the United States shall be deemed to be a "Disqualified Person."

"Personnel"	means other individuals under Sponsor-Principal Investigator's control and direction to whom specific Study responsibilities have been assigned.
"Protocol"	means the detailed description of the Study to be undertaken by the Sponsor-Principal Investigator included in the Proposal.
"Regulatory Authority"	means any national, international, or other governmental or industry agency or body with authority over the Study.
"Sponsor-Principal Investigator"	is the individual identified in the Preamble to this Agreement who has initiated and intends to conduct the Study, alone or with others. The obligations of the Sponsor-Principal Investigator include both those of a sponsor and those of an investigator in the Applicable Laws and Regulations. This term is intended to be consistent with the definitions of Sponsor and Investigator in the Applicable Laws and Regulations and the definition of Sponsor-Investigator in the ICH Guideline.
"Subject"	means an individual who participates in the Study.

2. Conduct of the Study; Institution and Sponsor-Principal Investigator Assurances

2.1. The Sponsor-Principal Investigator acknowledges and represents that he or she has initiated the Study and that the Study is not being run pursuant to a request from or on behalf of Alnylam.

2.2. The Parties hereby expressly acknowledge that Alnylam has no responsibility with respect to the initiation or management of the Study and is not, and shall not be held out as, a sponsor (as such term is defined under the Applicable Laws and Regulations), whether joint, sole or otherwise, of the Study.

2.3. The Institution (on behalf of itself and the Sponsor-Principal Investigator) and the Sponsor-Principal Investigator agree as follows:

2.3.1. Institution and Sponsor-Principal Investigator shall carry out the Study under the terms and conditions of this Agreement and the Protocol. The Protocol shall be consistent with the protocol included in the Proposal. Institution and Sponsor-Principal Investigator acknowledge that the decision by Alnylam to provide support for the Study was based on the Protocol submitted with the Proposal, including an analysis of the scientific merit of the Protocol. The Sponsor-Principal Investigator shall promptly notify Alnylam of any material changes to the Protocol or the suspension, premature termination of or conclusion of the Study. Continued support by Alnylam under the terms of this Agreement will be contingent on Alnylam's review and acceptance of any material changes to the Protocol.

2.3.2. The Sponsor-Principal Investigator shall act as the sponsor of the Study and shall assume all obligations of a sponsor, in addition to the obligations of a principal investigator, under the Applicable Laws and Regulations. The conduct and management of the Study, including the design of the Protocol and the receipt of all necessary licenses, approvals and/or allowances, shall be the sole responsibility of the Sponsor-Principal Investigator and the Institution. The Sponsor-Principal Investigator and the Institution shall not represent to any third party, including Subjects, that Alnylam is the sponsor of the Study.

2.3.3. Sponsor-Principal Investigator shall conduct the Study in full compliance with all Applicable Laws and Regulations and policies of the Institution and shall remain

responsible for such compliance throughout and after the conclusion of the Study.

2.3.4. As necessary, before commencing the Study, the Sponsor-Principal Investigator (and any sub-investigators, if applicable) shall obtain the necessary Institutional Review Board or ethics committee ("**IRB/EC**") approval and authorization to conduct the Study. Sponsor-Principal Investigator shall disclose to the IRB/EC that the Study is being supported by Alnylam. At Alnylam's request, Sponsor-Principal Investigator shall provide to Alnylam a copy of the correspondence from the IRB/EC approving and authorizing the conduct of the Study. Sponsor-Principal Investigator shall maintain the IRB/EC approvals, including obtaining appropriate continuing review of the Study by the IRB/EC, as required by the Protocol and by the Applicable Laws and Regulations.

2.3.5. Before commencing the Study, Sponsor-Principal Investigator shall obtain all necessary approvals and/or allowances from all Regulatory Authorities or other health authorities that have jurisdiction over the Study. Sponsor-Principal Investigator shall maintain the applicable Regulatory Authorities' and health authorities' approvals and/or allowances in good standing, and make all required regulatory filings, for the duration of the Study.

2.3.6. Neither Sponsor-Principal Investigator nor any sub-investigator, if applicable, shall enroll any Subject in the Study, or perform any Study-specific examination or procedure on a Subject, until such time as informed consent has been given by the Subject (or their legally authorized representative) in writing, as evidenced by a signed informed consent form from the Subject (or their legally authorized representative) in the form approved by the IRB/EC. Sponsor–Principal Investigator will ensure that a copy of the signed consent form is provided to the Study Subject. At Alnylam's request, Sponsor-Principal Investigator shall provide a copy of the informed consent form, the EC approval and any updates thereto.

2.3.7. Alnylam may audit Sponsor-Principal Investigator's and the Institution's records related to the Study at Institution's (or any other applicable) location at mutually agreeable times for the limited purpose of confirming that the Sponsor-Principal Investigator and Institution used the Support to conduct the Study in accordance with this Agreement.

2.3.8. The Sponsor-Principal Investigator and Institution shall ensure that all individuals involved in the performance of the Study possess the necessary qualifications and adhere to all professional standards applicable to the activities they shall or might reasonably be expected to undertake.

2.3.9. Sponsor-Principal Investigator shall submit to Alnylam abstracts, manuscripts and other proposed public disclosures of information or data related to the Study in accordance with the terms of Section 4 (Publication) below.

2.3.10. Within thirty (30) days of the earlier of the completion, termination or abandonment of the Study, the Sponsor-Principal Investigator shall submit to Alnylam a written report summarizing the Study data (the "**Study Report**"). The Sponsor-Principal Investigator shall make him/herself available to Alnylam, during business hours and on reasonable notice, to discuss in detail the Study Report.

2.3.11. Institution and Sponsor-Principal Investigator, as applicable, shall obtain and maintain insurance coverage for personal injury or death of Subjects which meets, at the very least, the minimum requirements prescribed by the Applicable Laws and Regulations and shall, upon request, provide copies of the applicable certificates of insurance to Alnylam as evidence of such insurance.

2.3.12. Institution and Sponsor-Principal Investigator will keep Alnylam advised of the status of

the Study through regular telephone conversations, yearly progress and efficiency reports, and meetings between Sponsor-Principal Investigator and Alnylam. Institution will obtain continuing review and approval by the IRB/EC of the Study as required by Applicable Law and Regulations and the policies of Institution.

3. Scope of Alnylam Support

3.1 In consideration for Institution's activities pursuant to this Agreement, including those obligations specifically undertaken by Institution and by Sponsor-Principal Investigator, Alnylam shall provide funding in an amount not to exceed **$133,000 USD** ("Support") as set forth in the budget and payment schedule in **Exhibit A**. Institution will be responsible for disbursement of Support to Sponsor-Principal Investigator for the Study.

3.2 This Support shall be used solely to conduct the Study. The amount detailed above represents the fair market value of the costs supported by Alnylam and have not been determined in a manner that takes into account the volume or value of any referrals or business. To the extent that the Study is not completed or supported activities are not performed, Institution and Sponsor-Principal Investigator agree to return to Alnylam any funds paid in advance by Alnylam for work not performed. Any such funds shall be returned to Alnylam within 30 days of Institution's and/or Sponsor-Principal Investigators' receipt of written notice from Alnylam detailing the amount of Alnylam's overpayment.

3.3 The Institution and the Sponsor-Principal Investigator acknowledge that the Support may not be sufficient for the total financing of the Study and nothing in this Agreement shall obligate Alnylam to provide any additional support or funding.

4. Publication

4.1. The Sponsor-Principal Investigator shall have the right to publish or otherwise publicly disclose information and data arising from the Study. Neither Institution nor Sponsor-Principal Investigator will, however, provide any such data or information to any third party for commercial benefit.

4.2. Before submitting information, data or results arising from the Study for publication (whether to a publisher, the public or otherwise, and irrespective of whether or not it is in draft or final form), the Sponsor-Principal Investigator shall provide a copy of the proposed disclosure (the "Disclosure"), to Alnylam for review at least sixty (60) calendar days prior to the earlier of submission to a third party for review or its publication or other disclosure. Such review shall consider solely whether the Disclosure discloses any inventions. Upon Alnylam's request, such Disclosure shall be further delayed for a period not to exceed ninety (90) calendar days to enable Alnylam to file any patent applications claiming any invention(s) disclosed in the Disclosure.

4.3. Alnylam confidential information shall not be included or disclosed in any publication or other public disclosure without Alnylam's express prior written consent.

4.4. The Sponsor-Principal Investigator agrees that any publication or other public disclosure shall include an acknowledgment of Alnylam's support of the Study and, if applicable, support of the development of the publication or disclosure.

4.5. Alnylam shall be entitled to make and use copies of the publication made by the Sponsor-Principal Investigator in relation to the Study.

4.6. This Section 4 shall survive the expiration or termination of this Agreement.

5. Intellectual Property & Data

5.1. The Institution or the Sponsor-Principal Investigator shall promptly notify Alnylam of any invention or technology or other intellectual property arising from the Study ("Study Intellectual Property"). The Institution and the Sponsor-Principal Investigator irrevocably grant to Alnylam (a) a royalty-free, nonexclusive, worldwide license, with the right to sublicense, to make, have made or use any invention or technology under any patent or other intellectual property rights covering such Study Intellectual Property and (b) a right of first refusal on any proposed sale or license of such Study Intellectual Property rights to any third party, such right to be exercised within 90 days after Alnylam receives written notice from the Institution or the Sponsor-Principal Investigator thereof. The Institution and the Sponsor-Principal Investigator shall promptly notify Alnylam of any such inventions or technology, or proposed sale or license thereof, with reference to this Agreement, and will provide such information as Alnylam may reasonably request from time to time to enable Alnylam to exercise its rights hereunder. Each of the Institution and the Sponsor-Principal Investigator represents and warrants that no other person will have any prior right to ownership of or a license under Study Intellectual Property by reason of any action, collaboration or agreement by the Institution or the Sponsor-Principal Investigator, respectively. Except as set forth above, no licenses or other rights are granted hereby by either party with respect to any inventions or technology.

5.2. All right, title and interest in and to (a) all data collected and databases generated in the performance of the Study, and (b) all compilations of data related to the Study (including the selection, coordination or arrangement of such data) that are created during the course of the Study belongs to and will remain the property of Institution and Sponsor-Principal Investigator. Alnylam and its agents shall have the unrestricted right to access and use any and all such documentation, data and information resulting from the Study without any additional compensation to Institution or Sponsor-Principal Investigator.

5.3. Institution and Sponsor-Principal Investigator will retain organized subject records, and laboratory records relating to the Study for the longer of (a) seven (7) years following completion or termination of the Study, (b) the period of time as may be required by Applicable Laws and Regulations, or (c) the period of time recommended in the current Good Clinical Practice Guidelines of the ICH.

6. Indemnification

6.1. The Parties acknowledge and agree that Alnylam is not the sponsor of the Study. Alnylam shall not be liable for any claim arising out of the Study, including, but not limited to, the design and conduct of the Protocol.

6.2. The Institution agrees to indemnify and hold harmless Alnylam with respect to any and all loss, damage, liability, legal fees and costs ("Losses") arising out of any (a) breach by the Institution of any of the terms of this Agreement, (b) injuries or damages (including death) alleged to be the result of the negligent or wilful act or failure to act of Institution, and (c) breach by the Institution of any statutory duty, including, without limitation, failure to properly obtain an appropriate informed consent from a Subject. For purposes of this Section 6.2, "Institution" shall mean, collectively, the Institution, the Sponsor-Principal Investigator, the Personnel and any other persons working under its, his or her supervision in the conduct of the Study.

7. Duration and Termination

7.1. The term of this Agreement shall commence on the Effective Date and shall terminate upon delivery of the final Study Report by the Sponsor-Principal Investigator to Alnylam, unless terminated earlier pursuant to this Section 7.

7.2. Alnylam, in its sole discretion, shall have the right to terminate this Agreement at any time, for any reason, upon sixty (60) days' prior notice to the Institution or the Sponsor-Principal Investigator.

7.3. This Agreement may be terminated by Alnylam or the Institution or the Sponsor-Principal Investigator (in any case, the "**Terminating Party**"), (i) if the Institution or the Sponsor-Principal Investigator, in the case of Alnylam, or Alnylam, in the case of Institution or Sponsor-Principal Investigator, commits a material breach of any of its obligations under this Agreement, and in the case of a breach which is capable of remedy, fails to remedy it within thirty (30) days of the receipt of notice from the Terminating Party specifying such breach, (ii) for Subject protection and safety considerations or (iii) upon a determination by such Party that there are no further benefits to be achieved from the Study or that continuation of the Study would be unethical.

7.4. Notices of termination must be in writing.

7.5. The following Sections hereof shall survive the expiration or termination of this Agreement: Section 4 (Publication), Section 5 (Intellectual Property & Data), Section 6 (Indemnification), this Section 7.5, Section 8 (Data Protection), Section 9 (Representations), Section 10 (Disqualification), and Section 11 (Miscellaneous).

8. Data Protection

8.1. The Parties shall comply with all applicable rules, regulations, guidelines and laws in Italy (together, the "***Data Protection Laws***"), as amended from time to time, regarding protection of personal data, including, but not limited to and if and as far as applicable to Italy, the guidance issued by the International Committee for Harmonization and the applicable international and country-specific privacy and data protection laws. Among other required actions, the Institution and the Sponsor-Principal shall perform any registrations with the local data protection authorities required under such Data Protection Laws.

8.2. **Parties Data**

8.2.1. Alnylam shall process the personal data (name and professional details) of the Sponsor-Principal Investigator and the Personnel solely for administrative, statistical, informative, and reporting purposes (including name, field of expertise, place of work and past experience with Alnylam) during the term of this Agreement and in relation to the conduct of the Study. The Sponsor-Principal consents to the transfer to Alnylam and its agents of his/her personal data. The Institution undertakes to inform the Personnel about the transfer of their personal data needed for the conduct of the Study.

8.2.2. Any personal data relating to the Institution, the Sponsor-Principal Investigator or the Personnel that may be contained in such processing will be used by Alnylam and its authorized Affiliates solely for the purposes of the performance of this Agreement. The Institution and the Sponsor-Principal Investigator acknowledge that some Alnylam entities may be located in countries where the data protection standards are not as protective as those in the country in which they usually perform their activities and, therefore, Alnylam shall ensure that such Alnylam entities will process the personal data in full compliance with the applicable law in Italy. Alnylam maintains adequate organizational and security measures to safeguard personal data from loss, misuse, unauthorized access, disclosure, alteration or destruction. Alnylam also maintains adequate procedures to help to ensure that such data is reliable for intended use, accurate, complete and current. Alnylam will honor rights of the relevant person to access and correct your data in accordance with the relevant Applicable Law. Alnylam acknowledges that the Institution, the Sponsor-

Principal Investigator and the Personnel have the right to review and modify or – after termination of the Study - request deletion of their personal data.

8.3. **Patient Data**

8.3.1. The Institution and Sponsor-Principal Investigator agree to comply with Applicable Laws and Regulations with respect to the confidentiality of Subjects' medical information and the protection of data which would allow identification of Subjects. Individually identifiable data of Subjects shall not be disclosed to Alnylam by the Institution or the Sponsor-Principal Investigator.

8.4. **Transparency**

8.4.1. In accordance with applicable laws, regulations and industry codes wherever such codes are applicable to Alnylam legal entities, the disclosure of transfers of value from pharmaceutical manufacturers to Healthcare Organizations (HCOs), may be required. Institution and Investigator acknowledge and agree that Alnylam may have certain disclosure and reporting obligations pursuant to such applicable laws, regulations and relevant industry codes, including, but not limited to, the disclosure and reporting of fees and amounts payable pursuant to this Agreement.

8.4.2. Institution and Sponsor-Principal Investigator shall report to Alnylam any such information as needed to be compliant with its reporting obligations under applicable laws, regulations and industry codes, including but limited to monetary funding and non-monetary benefits received, fees and any other direct or any indirect costs paid by Alnylam under this Agreement. Alnylam shall have the right to review receipts and other documentation of Institution and Investigator related to such information subject to its reporting obligations.

9. Representations

9.1. The Institution and the Sponsor-Principal Investigator represent and warrant that they have obtained the requisite approvals to execute this Agreement and conduct the Study. The Institution represents and warrants that it has the authority to require the Sponsor-Principal Investigator to comply with the terms of the Agreement and that the performance of activities under this Agreement by the Sponsor-Principal Investigator or any Personnel or other staff to which such activities are delegated does not violate institutional policy.

9.2. Without limiting the generality of the foregoing, Institution and Sponsor-Principal Investigator each represent and warrant that (a) the Study (and Protocol) has been reviewed and approved by Institution's internal scientific review and ethics committees, (b) the Sponsor-Principal Investigator has the expertise and experience necessary to conduct the Study, including clinical expertise in the clinical area and experience in undertaking comparable clinical research, (c) Institution has the administrative infrastructure, clinical and administrative personnel and resources to undertake the Study and regularly conducts comparable clinical research, and (d) sufficient funding has been allocated to the Study, including the funding provided by Alnylam under this Agreement, to conduct the Study.

9.3. The Parties acknowledge, agree and represent that the purpose of this Agreement is to allow for scientific research and not to promote or influence the sale or purchase of any Alnylam products, now or in the future, and that this Agreement is not part of any other arrangement, express or implied, pursuant to which the Institution or the Sponsor-Principal Investigator are obliged to buy, prescribe, provide favourable formulary status for, or otherwise promote or support Alnylam products.

10. Disqualification

10.1 The Institution represents and warrants that neither it nor the Sponsor-Principal Investigator, nor any Personnel, have ever been and are not currently Disqualified Persons, nor will the Institution employ any Disqualified Persons. The Institution or the Sponsor-Principal Investigator shall notify Alnylam immediately if it, he or she becomes aware of any contrary information. The Institution represents and warrants that the Sponsor-Principal Investigator and the Personnel have not engaged in any conduct or activity which could lead to any of the above-mentioned disqualification actions and that it has no notice that any Regulatory Authority intends to seek any such disqualification. If during the term of this Agreement, the Institution, the Sponsor-Principal Investigator or any Personnel (a) comes under investigation by any Regulatory Authority for any disqualification action, (b) is disqualified, or (c) engages in any conduct or activity which could lead to any of the above-mentioned disqualification actions, the Institution shall immediately notify Alnylam of the same.

10.2 In the event the Sponsor-Principal Investigator is unable or unwilling to carry out his/her duties under the Protocol for any reason, Institution may nominate a replacement for the Sponsor-Principal Investigator. If Alnylam does not approve the replacement within thirty (30) days after receipt of notice from the Institution, the Study and this Agreement will terminate.

11. Miscellaneous

11.1. This Agreement shall not create any relationship of employment between Alnylam and the other Parties or an agency, contractor or partnership, respectively, between Alnylam and the other Parties and shall not give any Party any authority to bind the respective other Parties. Neither the Institution nor the Sponsor-Principal Investigator shall use Alnylam's name in connection with any notification or other publication without the prior written consent of Alnylam.

11.2. The obligations under this Agreement are personal to the Institution and the Sponsor-Principal Investigator and neither this Agreement nor any right or obligation hereunder may be assigned, transferred or subcontracted by the Institution or the Sponsor-Principal Investigator to another party. Alnylam reserves the right to assign all or part of its rights and obligations hereunder to its Affiliates or in connection with the sale or transfer of all or substantially all of its assets.

11.3. If a court of competent jurisdiction holds that any term of this Agreement is unenforceable, illegal or void, such term shall be enforced only to the extent that it is otherwise enforceable or is not in violation of such law, and all other terms of this Agreement shall remain in full force and effect.

11.4. This Agreement (a) may be executed in counterparts, each of which shall be deemed to be an original and all of which, taken together, shall constitute a single agreement binding on all Parties, and (b) will be considered executed by a Party when the signature of such Party is delivered physically or by email or facsimile transmission to the other Party or Parties, as appropriate. The Parties agree that any signature delivered by email or facsimile transmission shall have the same force and effect as an original signature.

11.5. Any amendment or change of this Agreement shall only be effective if made in writing and executed by each and all of the Parties hereto. For the avoidance of doubt, email shall not constitute writing for the purpose of this Section 11.5.

11.6. This Agreement and any schedule, exhibit or other documents, including the Protocol, referred to in this Agreement, shall constitute the entire agreement between the Parties with regard to the subject matter herein. Each Party acknowledges that in entering into this Agreement, it does not rely on any other promise, warranty or other provision except as expressly provided for in this Agreement and that all conditions, warranties and other terms implied by statute or implicitly are hereby excluded to the fullest extent permitted by law.

11.7. Nothing in this Agreement shall confer any rights upon any person or entity who is not a Party to

this Agreement.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed and made effective as of the Effective Date.

Alnylam Pharmaceuticals, Inc.

By: Kevin Huestis
[signature]

Name: Kevin Huestis
Title: Sr. Director, Procurement
Date: 11-Jun-2018 | 08:24 EDT

Institution:
University of Heidelberg

By: i. A.
[signature]

Imtraut Gürkan
Kaufmännische Direktorin
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 672 · 69120 Heidelberg

Name:
Title:
Date: 25.05.2018

Sponsor-Principal Investigator

[signature]

Name: Professor Arnt Kristen, M.D.
Date:

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18.05.18

EXHIBIT A

Study Budget and Payment Schedule

Total cost / budget

i. personnel:	physician 20%	US $	12,000
	lab technician 50%	US $	15,000
ii. biomarker kits (120 patients approximately $ 400 each)		US $	68,000
Total costs		**US $**	**95,000**

The institutional overhead costs are defined as 40% of the study budget.

Total budget (study budget + overhead costs) **US $ 133,000**

Payment Schedule

Institutional shall receive 25% percent of the total budget in accordance with meeting the milestones listed below:

- Milestone 1: Contract execution and IRB approval
- Milestone 2: Samples collected from the 120th patient
- Milestone 3: Completion of biomarker analysis
- Milestone 4: Final report

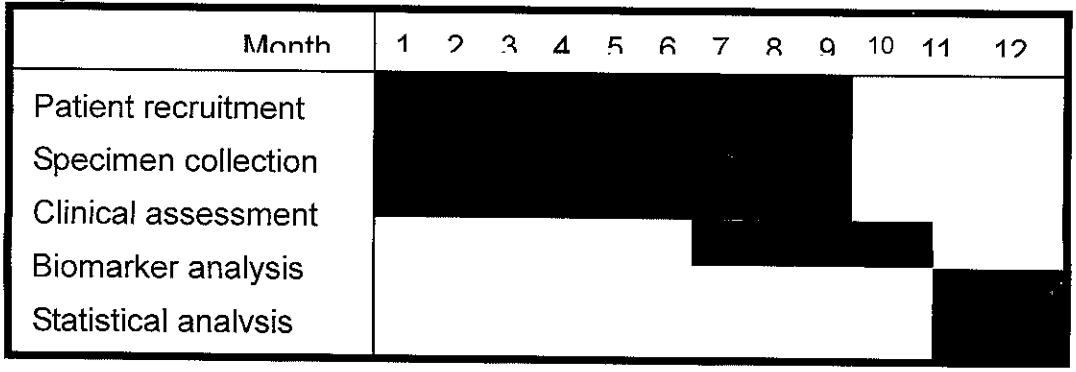
EXHIBIT B
Proposal

Specific Aims

This study is aimed to advance medical knowledge in diagnosis, clinical management and hopefully outcome of patients with different genotypes and phenotypes of ATTR amyloidosis. Moreover, it might be helpful for diagnostic purposes at initial diagnosis of ATTR amyloidosis by establishment of a set of biomarkers defining disease severity (and potentially outcome) even in asymptomatic carriers of a transthyretin gene variant. Whether the levels of individual biomarkers in blood are predictive of disease severity and clinical course of systemic ATTR amyloidosis or not will be tested by prospective measurement of a set of biomarkers in patients with immunohistochemical evidence of ATTR amyloid. Moreover, asymptomatic carriers of transthyretin variants, and patients with wild-type ATTR amyloidosis will be included. Levels of biomarkers will be compared with asymptomatic carriers of transthyretin gene variants and age-matched healthy controls. At our Center all patients are followed systematically. Thus, we will be able to assess the prognostic value of these findings in future research.

The current study is based on the hypothesis that a combination of diverse biomarkers in blood obtained from patients with diverse genotypes and phenotypes of ATTR amyloidosis are helpful to define disease severity (and potentially to predict outcome). Finally, a single biomarker or a combination of diverse biomarkers in ATTR amyloidosis might be more sensitive in predicting future occurrence of ATTR amyloidosis in obviously asymptomatic carriers of transthyretin variants and thus might be the clue for early diagnosis of this progressive and finally fatal disease.

Study duration



Study Objective(s)

The overall objective of this study is to evaluate the clinical value of diverse biomarkers in blood obtained from patients with different genotypes and phenotypes of ATTR amyloidosis.

Specific objectives are:

i) To assess novel biomarkers in blood of patients with hereditary transthyretin amyloidosis.

More than 100 different point mutations have been reported to cause hereditary ATTR amyloidosis manifesting in a wide heterogeneity of clinical phenotypes. Cardiac and neurological symptoms are the most common findings with some patients displaying either cardiac or neurological symptoms, and others with combination of both.
Serum samples of all patients will be used for measurement of diverse biomarkers established for other forms of heart failure, including dilated cardiomyopathy, hypertrophic, and hypertensive cardiomyopathy, and/or have already been established for evaluation of disease severity and outcome in systemic light-chain amyloidosis.

ii) To assess novel biomarkers in blood of patients with wild-type ATTR amyloidosis

Aside from hereditary ATTR amyloidosis, deposition of wild-type transthyretin amyloid in the heart is common among

patients older than 70 years of age. Since the age of onset of wild-type ATTR amyloidosis differs from hereditary forms of ATTR amyloidosis, we hypothesize that results of biomarker measurements might differ when compared to mutant-type amyloidosis patients with cardiac manifestation. Blood samples obtained from a cohort of patients with wild-type ATTR amyloidosis will be analyzed in parallel to samples of patients with hereditary ATTR amyloidosis and compared to results of the cardiac group.

iii) To correlate biomarkers with clinical parameters (and outcome in future research beyond the scope of this proposal) in patients with ATTR amyloidosis
Results of biomarkers in patients with ATTR amyloidosis will be correlated with broad clinical data available at our center due to extensive routine evaluation. Individual markers will be used for classification of disease severity (and in future research ultimately prediction of outcome). Particularly, biomarker levels of patients with cardiac manifestation will be divided into the diverse transthyretin variants (if the number of patients for a single variant is accurate) and will be compared to wild-type ATTR patients.
Beyond the scope of this study, this approach is an important step for important future research.
This research includes:

iv) Mid-term future perspectives (beyond this funding): To correlate the present findings with clinical outcome of ATTR amyloidosis patients and to establish optimal biomarker combination for prediction of outcome in patients with ATTR amyloidosis.
Through the described project, we expect to gain highly valuable and novel insights into potential predictors of disease severity and outcome in different genotypes and phenotypes of ATTR amyloidosis. This data might be helpful for the diagnostic work-up of patients with ATTR amyloidosis regarding prediction of organ involvement and mortality.

v) Long-term future perspectives (beyond this funding period): To longitudinally assess the blood levels of biomarkers with clinical findings in asymptomatic carriers of a transthyretin gene variant and to establish an optimal biomarker combination for early identification of symptomatic ATTR amyloidosis.

Patient Population
Inclusion criteria: patients at least 18 years of age diagnosed with wild-type or mutant-type ATTR amyloidosis with cardiac and/or neurological manifestation. Plasma samples will prospectively be collected from patients with newly diagnosed symptomatic hereditary ATTR amyloidosis and patients will be divided in the following groups:

- Mutant-type ATTR amyloidosis with cardiomyopathy
- Mutant-type ATTR amyloidosis with polyneuropathy
- Mutant-type ATTR amyloidosis with cardiac and neurologic phenotype
- Carrier of TTR gene variant without any symptoms
- Wild-type ATTR amyloidosis
- Age-matched healthy controls

Exclusion criteria: patients with amyloid types other than ATTR amyloidosis or patients that have been enrolled in a placebo-controlled clinical trial.

Study Design
The proposed prospective study derives from a population of patients subsequently undergoing detailed evaluation at a large European tertiary amyloidosis referral center. During routine visits patients will be asked for an additional blood samples that will be analyzed in the proposed project. Four 7.5 ml samples will be collected and plasma prepared following standard procedure applying 1500 g centrifugation for 10 minutes. Samples will be stored in aliquots at -20°C until further biomarker analyses as explained in detail above.

Clinical routine assessment will include collection of demographic data, clinical examination and laboratory testing including routine cardiac biomarkers (NT-proBNP, high-sensitivity Troponin T). Routine cardiac testing includes non-

invasive testing by electrocardiography and echocardiography including post-processing for strain analyses.
Blood samples will be analyzed in duplicates by the use of Luminex assay as well as established specific biomarker assays according to the manufacturer's instruction including:

- blood proteomic profiling (Luminex Assay, R&D Systems Inc, Minneapolis, USA) including a set of heterogenous markers related to myocyte injury, myocardial stretch, matrix remodeling, inflammation, oxidative stress
- high-sensitive troponins (Elecsys hs-TnT immunoassay, Roche Diagnostics, Germany)
- mid-regional proatrial natriuretic peptide (MR-proANPLIA, B.R.A.H.M.S. GmbH, Germany)
- n-terminal pro-B-type natriuretic peptide (Elecsys proBNP immunoassay, Roche Diagnostics, Germany)
- adrenomedullin (B.R.A.H.M.S. GmbH, Germany)
- heart-type fatty acid-binding protein (immunoturbidimetric assay, Randox Laboratories Ltd., Crumlin, UK)
- copeptin (Kryptor ultrasensitive assay; Thermo Fisher Scientific BRAHMS, Germany)

Outcome measures:
(a) The primary outcome will evaluate the level of individual biomarkers in blood in the individual cohorts of patients with ATTR amyloidosis.

(b) The secondary outcome measure is the comparison of individual serum levels of biomarkers with clinical findings indicating severity of ATTR amyloidosis observed at initial presentation of the patients at our center. Routine assessment includes electrocardiography (low voltage pattern, atrio-ventricular conduction delay, any bundle branch block, pseudoinfarction pattern, abnormal repolarization), echocardiography morphological (atrial volumes, ventricular volumes, wall thickness) and functional analyses (ejection fraction, diastolic function, longitudinal function) including strain rate imaging (global longitudinal strain, regional strain rate) and laboratory findings (NT-proBNP, high-sensitivity troponin T).

(c) Tertiary outcome measures of future research are the correlation of biomarker levels with survival as well as the role of biomarker levels for early diagnosis of the disease in asymptomatic carriers of a transthyretin gene variant.

Data collected
During routine visits patients will be asked for an additional blood samples that will be analyzed in the proposed project. Four 7.5 ml samples will be collected and plasma prepared following standard procedure applying 1500 g centrifugation for 10 minutes. Samples will be aliquoted and stored at -20°C. Serum samples of all patients will be used for measurement of diverse biomarkers obtained in other forms of heart failure, including dilated cardiomyopathy, hypertrophic, and hypertensive cardiomyopathy, and/or have already been established for evaluation of disease severity and outcome in systemic light-chain amyloidosis.

Clinical routine assessment will include collection of demographic data, clinical examination and laboratory testings including routine cardiac biomarkers (NT-proBNP, high-sensitivity Troponin T). Routine cardiac testing includes non-invasive testing by electrocardiography and echocardiography including post-processing for strain analyses.