TEMPLATE CLINICAL TRIAL AGREEMENT

Scope of use:

This template clinical trial 3-way agreement is created in joint cooperation between the vereniging Samenwerkende Topklinische opleidingsZiekenhuizen (STZ) in the Netherlands en Nefarma to facilitate conducting clinical trials in The Netherlands. This contract meets the Guidelines of the CCMO.

CLINICAL TRIAL AGREEMENT

The undersigned,

A. [*insert name of the sponsor*], whose registered office is at [*insert address*], lawfully represented by [*insert name(s) and function(s)*]
(hereinafter referred to as "**Sponsor**")

and

B. [*insert name of institution*], whose address is at [*insert address*], lawfully represented by [*insert name(s) and function(s)*]
(hereinafter referred to as "**Institution**")

and

C. [INVESTIGATOR], [*insert: name of physician …», …[function], [tax/office address and chamber of commerce registration number, if applicable*]
(hereinafter referred to as "**Principal Investigator**")

WHEREAS, the Sponsor is a pharmaceutical company involved in research, development, registration, manufacture and/or sale of medicines for use in humans;

WHEREAS, the Sponsor has designed the clinical trial identified hereof, to evaluate Sponsor's drug _____ ("Study Drug") in accordance with the protocol entitled _____; and

WHEREAS, the Principal Investigator and Institution are concerned with the diagnosis, treatment and prevention of disease and/or clinical research for the improvement of healthcare;

WHEREAS, the Institution has facilities and personnel with the requisite skills, experience, and knowledge required to support the performance of the clinical trial by the Principal Investigator; and

WHEREAS, Principal Investigator, having reviewed the Protocol for the Clinical Trial, the investigator brochure and sufficient information regarding the Investigational Product in order to evaluate and determine its interest in participating in the Clinical Trial, wishes to participate in the Clinical Trial and the Principal Investigator assures that he/she has sufficient authority, competence and experience in conducting clinical trials.

In consideration of the undertakings and commitments set forth herein, the Parties agree to enter into this Clinical Trial Agreement.

1. DEFINITIONS

The following words and phrases have the following meanings:

a. "**Affiliate**" means any business entity which controls, is controlled by, or is under the common control with Sponsor. For the purposes of this definition, a business entity shall be deemed to control another business entity if it owns, directly or indirectly, in excess of 50% of the voting interest in such business entity or the power to direct the management of such business entity or to elect or appoint 50% or more of the members of the management of such business entity;

b. "**Agent**" shall include, but shall not be limited to, any person providing services to a Party under a contract for services or otherwise, to include without limitation any pharmacist, clinical chemist, nurse or other health professional.

c. "**Agreement**" means this agreement comprising its clauses, schedules and any appendices attached to it, including the Protocol and including any amendments to the Agreement agreed between the Parties;

d. "**Auditor**" means a person who is authorised to carry out a systematic review and independent examination of clinical trial related activities and documents to determine whether the evaluated clinical trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the Protocol, the Sponsor's Standard Operating Procedures, ICH GCP and the applicable regulatory requirements;

e. "Clinical Data" means personal data as defined in Directive 95/46/EC and in the Dutch privacy Law, i.e. any information relating to an identified or identifiable Clinical Trial Subject.

f. "**Clinical Trial**" means the investigation to be conducted at the Trial Site in accordance with the Protocol as mentioned above;

g. "**Clinical Trial Authorisation**" means a Clinical Trial authorised in accordance with the article 2 and 13i of the Dutch *Medical Research Involving Human Subjects Act*;

h. "**Clinical Trial Subject**" means a person enrolled to participate in the Clinical Trial;

i. "**Competent Authority**" means the authority appointed to evaluate the Clinical Trial in accordance with 13i of the Dutch *Medical Research Involving Humans Subjects Act*, based on article 9 of the European Clinical Trial Directive 2001/20/EC;

j. "**Confidential Information**" means any and all information, data and material of any nature belonging or entrusted to a Party and/or its Affiliates, or which is a trade secret, which such Party (the "Disclosing Party") may disclose in any form to the other Parties (each a "Recipient") pursuant to this Agreement, the release of which is likely to prejudice the interests of the Disclosing Party;

k. "**CRF**" means the case report form in a format prepared by Sponsor and documenting the administration of the Investigational Product to Clinical Trial Subjects as well as all tests and observations related to the Clinical Trial;

l. "**eCRF**" means a CRF in electronic form;

m. "**DSMB**" means a group of individuals with pertinent expertise that have oversight of and reviews on a regular basis accumulating data from one or more ongoing clinical trials and that advise the Sponsor regarding the continuing safety of Clinical Trial Subjects and those to be recruited to the Clinical Trial, as well as the continuing validity and scientific merit of the Clinical Trial.
n. "**Effective Date**" the date this Agreement comes into effect, being the date of the last Party's signature to this Agreement;
o. "**Ethics Committee**" means the accredited medical research ethics committee competent to review the Clinical Trial in accordance with applicable Law, and to which the Protocol has been submitted for approval;
p. "**Intellectual Property Rights**" means patents, trade marks, trade names, service marks, domain names, copyrights, rights in and to databases (including rights to prevent the extraction or reutilisation of information from a database), design rights, topography rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere in the world, whether or not any of them are registered and including applications for registration of any of them;
q. "**Investigational Product**" means the Study Drug identified above and the control material, as further detailed in the Protocol;
r. "**Know How**" means all technical and other information which is not in the public domain (other than as a result of a breach of confidence), including but not limited to information comprising or relating to concepts, discoveries, data, designs, formulae, ideas, inventions, methods, models, procedures, designs for experiments and tests and results of experimentation and testing, processes, specifications and techniques, laboratory records, manufacturing data and information contained in submissions to regulatory authorities, whether or not protected by Intellectual Property Rights or any applications for such rights;
s. "**Law**" means any International, European Union and Dutch law and regulations, as well as generally accepted international conventions applicable to the performance of the Clinical Trial. Such Law including:
    - Directives 2001/20/EC and 2005/28/EC of the European Parliament and the Council relating to medicinal products for human use and in guidance published by the European Commission pursuant to such Directives and any implementation in Institution's national Law,
    - The Council Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data and any implementation in Institution's national Law,
    - the Dutch Medical Research Involving Human Subjects Act (*Wet Medisch-wetenschappelijk Onderzoek met Mensen* or *WMO*),
    - the Dutch Personal Data protection Act (*Wet Bescherming Persoonsgegevens)*
    - the Dutch Medical Treatment Agreements Act (*Wet op de geneeskundige behandelingsovereenkomst* or *Wgbo*)

- ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95),
- the Directives on "Review of Clinical Trial Agreements" and on "External Review" issued by the Dutch Central Committee on Research involving Human Subjects (*Centrale Commissie Mensgebonden Onderzoek* or *CCMO*),
- the principles of the Dutch Code of Conduct regarding the adequate procurement, management and use of bodily human tissue published by the Federation of Dutch Medical Scientific Societies,
- the Code of Federal Regulations of the U.S. Food and Drug Administration (FDA) to the extent applicable to the Clinical Trial, and
- the Nefarma gedragscode farmaceutische bedrijfstak, applicable for the Sponsor, and
- References to EU Council Directives and Dutch Law include any amendments or replacements of such Law.

t. "**Party**" means the Sponsor, the Institution or the Principal Investigator and "Parties" shall mean two or all of them jointly;

u. "**Principal Investigator**" means the person who will take primary responsibility for the conduct of the Clinical Trial at the Trial Site or any other person as may be agreed from time to time between the Parties as a replacement;

v. "**Protocol**" means the document signed by the Principal Investigator, entitled "[insert protocol name]" with registration [*insert EUDRACT number or Dutch Registration NL-number and date]* detailing all aspects of the Clinical Trial, a copy of which is at Annex 1 to this Agreement. The Protocol includes all amendments thereto for which Clinical Trial Authorisation has been obtained;

w. "**Research Staff**" means the persons who will undertake the conduct of the Clinical Trial at the Trial Site on behalf of the Principal Investigator and under the supervision of the Principal Investigator;

x. "**Samples**" means any human biological materials, including but not limited to blood, body tissue, plasma and any other material containing human cells;

y. "**Site Parties**" shall refer to the Principal Investigator and the Institution jointly;

z. "**Target**" means the estimated number of Clinical Trial Subjects to be included in the Clinical Trial as referred to in clause 5.2;

aa. "**Timelines**" means the dates set out in Annex 2 hereto as may be amended by agreement between the Sponsor and the Principal Investigator and "**Timeline"** shall mean any one of such dates;

bb. "**Trial Monitor**" means one or more persons appointed by the Sponsor to monitor compliance of the Clinical Trial with GCP and the Protocol and to conduct source data verification;

cc. "**Trial Site(s)**" means the premises at the department [ ] of the [ ][*please confirm and precise the location*] where the Clinical Trial will be conducted;

2. OBLIGATIONS

2.1. The Sponsor and the Principal Investigator agree to perform the Clinical Trial in accordance with the terms and conditions of this Agreement.

2.2. The Site Parties represent and warrant that they each have the authority to enter into this Agreement. The Principal Investigator will ensure the availability of and/or access to any resources necessary to perform the Clinical Trial at the Trial Site, including departments, facilities and Research Staff and support personnel, and represents that he/she holds the necessary registration and has the necessary qualifications, expertise and time to perform the Clinical Trial.

2.3. The Principal Investigator shall notify the Sponsor if he/she ceases to be associated with the Institution where the Clinical Trial will be conducted or if he/she is otherwise unavailable to continue as Principal Investigator, and Principal Investigator shall use all reasonable endeavours to find a qualified successor acceptable to the Sponsor, subject to the Principal Investigator's overriding obligations in relation to Clinical Trial Subjects and individual patient care. In the event Principal Investigator is for whatever reason unable or unwilling to appoint a successor personally, the Institution will have the right to recommend a suitable successor. If subject to the foregoing no mutually acceptable replacement can be found, within reasonable time as not to hinder the safe continuation of the Clinical Trial at the Trial Site, and safe that the Sponsor will not unreasonable withhold its approval of the proposed replacement of Principal Investigator, each Party may terminate this Agreement pursuant to clause 12.3 below without further liability to each other, except for the responsibility of the Sponsor subject to clause 12.4 hereof.

2.4. The Principal Investigator shall procure the performance of the obligations of the Research Staff as set out in this Agreement.

2.5. Subject to the Principal Investigator's overriding obligations in relation to Clinical Trial Subjects and individual patient care, the Principal Investigator shall not, and the Principal Investigator shall ensure that the Research Staff shall not, during the term of this Agreement conduct any other trial which might jeopardize the Principal Investigator's ability to recruit, enrol and study the required cohort of Clinical Trial Subjects.

2.6. The Principal Investigator and the Institution acknowledge that Sponsor and its Affiliates need to adhere to the provisions of (i) the Bribery Act 2010 of the United Kingdom (***Bribery Act***); (ii) the Foreign Corrupt Practices Act 1977 of the United States of America (***FCPA***) and (iii) any other applicable anti-corruption legislation (together the ***Applicable Anti-Corruption Legislation***). A summary of the key principles underlying the Bribery Act and the FCPA is set out in Annex 6. The Institution and the Principal Investigator shall not and shall not permit or induce employees, agents, consultants or other representatives, whether directly or indirectly, to engage in any activity that is prohibited by the Applicable Anti-Corruption Legislation including bribery, kickbacks, payoffs or other corrupt business practices

3. CLINICAL TRIAL GOVERNANCE AND COMPLIANCE

3.1. The Sponsor shall be responsible for obtaining and maintaining Clinical Trial Authorisation for the Clinical Trial and substantial amendments to the Protocol. The Sponsor may require the Principal Investigator to apply for the Clinical Trial Authorisation for Sponsor, in which case the Principal Investigator shall keep the Sponsor fully apprised of the progress of Ethics Committee submissions and shall upon request provide the Sponsor with all correspondence relating to such submissions.

3.2. The Principal Investigator shall not consent to any change in the Protocol requested by the Ethics Committee or Competent Authority without the prior written consent of the Sponsor.

3.3. In the event of any substantial amendments being made to the Protocol, the amendments shall be signed by the Principal Investigator and shall be implemented by the Research Staff as required by the Sponsor after approval of the amendments by the competent authority(ies) and a favourable opinion of the Ethics Committee.

3.4. The Clinical Trial shall be performed at the Trial Site. The Principal Investigator shall be responsible for obtaining authorization from the representatives of the Trial Site to perform the Clinical Trial at the Trial Site, which shall include but not be limited to the engagement of sub-investigators, to the extent applicable the pharmacist of the Institution, clinical chemists, and the Research Staff required to perform the Clinical Trial as set out in this Agreement.

3.5. The Sponsor shall submit the Clinical Trial for listing on a free, publicly accessible clinical trial registry like www.clinicaltrials.gov or on websites managed by a registry conforming to WHO standards (http://www.who.int/ictrp/network/criteria_summary/en/index.html) after Clinical Trial Authorization. Upon request of the Institution or the Principal Investigator the Sponsor will disclose the registry and the date of submission.

3.6. The Principal Investigator hereby represents, warrants and covenants that he/she has obtained and shall maintain all necessary authorizations from the Trial Site representatives to perform the Clinical Trial.

3.7. The Parties shall conduct the Clinical Trial in accordance with:

a. the Agreement;

b. the terms and conditions of the Clinical Trial Authorisation granted by Competent Authority and the opinion of the Ethics Committee; and

c. the applicable Law

4. LIABILITIES, INDEMNIFICATION AND INSURANCE

4.1. Subject to the limitations set out hereinafter, Sponsor shall indemnify and hold harmless Institution, its employees, the Principal Investigator and the Research Staff (the "Indemnitees") against all claims, demands, actions or proceedings (to

include any settlements or ex gratia payments made with the consent of the Parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise): (i) by or on behalf of any Clinical Trial Subject for personal injury or death arising out of the administration or use of the Study Drug during or as a result of the Clinical Trial, or to any clinical intervention or procedure provided for or required by the Protocol, to which the Clinical Trial Subject would not have been exposed but for its participation in the Clinical Trial; (ii) by Institution, its employees, the Principal Investigator or by or on behalf of a Clinical Trial Subject for compensation of reasonable and necessary medical costs and expenses incurred by the Clinical Trial Subject who has suffered such personal injury.

4.2. Sponsor's indemnification and defence of the Indemnities shall not apply to any claim or proceeding pursuant to clause 4.1, and Sponsor shall not be liable:

(a) to the extent that said personal injury (including death) is caused by any of the Indemnities' failure to comply with this Agreement; or

(b) to the extent that said personal injury (including death) is caused by (medical or other) professional malpractice, negligence, recklessness or deliberate misconduct (in Dutch: *beroepsfout, nalatigheid, roekeloosheid of opzettelijk handelen of nalaten*) of any of the Indemnities;

(c) if any of the Indemnities shall have made any admission in respect of such claim or proceeding or taken any action relating to such claim or proceeding prejudicial to the defence of it, without the written consent of Sponsor, such consent not to be unreasonably withheld, provided that this condition shall not be treated as breached by any statement properly made by any of the Indemnities in connection with the operation of Institution's internal complaint procedures, accident reporting procedures or disciplinary procedures or where such a statement is required by law.

4.3. Sponsor shall keep Institution and the Principal Investigator reasonably informed of the progress of any such claim or proceeding.

4.4. The Parties will each use its reasonable endeavours to inform each other promptly of any circumstances reasonably thought likely to give rise to any claim or proceeding resulting from the Clinical Trial of which it is directly aware. Parties shall keep each other reasonably informed of developments in relation to any such claim or proceeding. The Parties will consult with each other on the nature of any defence to be advanced.

4.5. Institution, Principal Investigator and Sponsor will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding made or brought by or on behalf of Clinical Trial Subjects (or their dependants).

4.6. Nothing in this clause 4 shall operate so as to restrict or exclude the liability of any Party vis-à-vis the Clinical Trial Subjects in relation to their death or personal

injury caused by the negligence of that Party or its servants or employees or to restrict or exclude any other liability of a Party which cannot be so restricted or excluded in law.

4.7. In no circumstances shall any Party be liable to the other in contract, tort or otherwise howsoever arising or whatever the cause thereof, for any indirect or consequential damages of any nature, such as but not limited to any loss of profit, business, goodwill, reputation, contracts, revenues or anticipated savings which arise directly or indirectly from any default on the part of Sponsor, Institution or the Principal Investigator, except and to the extent such damages (a) shall be covered under and paid out of any insurance policy of the liable party, or (b) result from negligence, recklessness or deliberate misconduct of the liable party or their employees, officers, Agents or other auxiliary persons (in Dutch: *hulppersonen*).

4.8. The liability of the Institution for a claim or proceeding of Sponsor under clause 4.7 shall be limited to the maximum amount covered under the insurance policy as generally applicable for such claim or proceeding or to euro one million (€ 1,000,000) whichever amount is the highest.

4.9. In the case of equipment loaned or otherwise made available by or on behalf of Sponsor to Institution for the purposes of the Clinical Trial, Institution's liability for damages or loss of the equipment arising from its negligence or from negligence of its Agents or auxiliary persons shall exclude fair wear and tear and shall not exceed the value of the equipment.

4.10. Sponsor will take out or maintain (a) insurance cover in respect of its potential liability for damages to Clinical Trial Subjects resulting from the Clinical Trial in accordance with the requirements set out in the (Dutch) *Medical Research Involving Human Subjects Act* and the *Decree on Obligatory Insurance for Medical Studies involving Human Subjects* unless this requirement has been waived by the Ethics Committee, and (b) further appropriate insurance cover in respect of its other potential liability under this Agreement. Sponsor shall produce to Institution, on request, copies of such insurance certificates. Without prejudice to the limitations stated in clause 4.7 above, the terms of any insurance or the amount of cover shall not relieve Sponsor of any liabilities under this Agreement.

4.11. Institution will take out or maintain an insurance cover in respect of the potential liability of Institution, the Research Staff, the Principal Investigator and any other employees involved with the conduct of the Clinical Trial pursuant to this Agreement. Institution shall produce to Sponsor, on request, copies of insurance certificates, together with evidence that the policies to which they refer remain in full force and effect during the term of this Agreement and any period thereafter as may be required by mandatory law. Without prejudice to the limitations stated in clause 4.7 and 4.8 above, the terms of any insurance or the amount of cover shall not relieve Institution or the Principal Investigator of any liabilities under this Agreement.

5. CLINICAL TRIAL SUBJECT RECRUITMENT AND ENROLLMENT

5.1. The Principal Investigator shall make sure that the Clinical Trial Subjects (and/or their legal representatives) will, in accordance with applicable Law, be duly informed and that each give his informed consent prior to his participation in the Clinical Trial.

5.2. The Principal Investigator shall use reasonable endeavours to recruit the Target within the Timelines as specified in Annex 2. As soon as the Principal Investigator expects to reach the Target, he shall notify the Sponsor. Likewise, in case the Principal Investigator expects that the Target will not be reached within the given Timelines, he shall notify Sponsor accordingly, and the Parties shall discuss the consequences.

5.3. If circumstances or events have occurred or will occur that will substantially delay or are likely to substantially delay the progress of recruitment or enrolment of the Clinical Trial Subjects, the Principal Investigator shall immediately inform the Sponsor in writing. In each such event the Parties shall discuss the consequences of the delay and each Party shall undertake reasonable endeavours to agree on measures to overcome the delay.

5.4. In the event that the Clinical Trial is part of a multi-centre clinical trial, the Sponsor may amend the number of Clinical Trial Subjects to be recruited pursuant to the Target as per clause 5.2 above subject to this clause 5.4.

(a) The Sponsor may require further recruitment of Clinical Trial Subjects at the Trial Site to cease if:

- in the reasonable opinion of the Sponsor recruitment of Clinical Trial Subjects at the Trial Site will not meet or will not likely meet the Target within the Timelines or is proceeding at a rate below that required to enable the relevant Timeline to be met, and upon Sponsor's request to increase the inclusion rate, the Principal Investigator is unable to comply, or
- if the global recruitment target for all clinical centres of Sponsor and its affiliates has been reached.

Upon receipt of a notice subject to clause 5.4 (a), the Principal Investigator shall immediately stop the recruitment and inclusion of Clinical Trial Subjects and the terms and conditions of this Agreement shall not apply to individuals who, at the time of receipt of such notice, have not signed informed consent and have not been included in the Clinical Trial. Payments shall only be made according to the number of Clinical Trial Subjects recruited and included up to the date of receipt of the notice. The Sponsor will not take any responsibility or have a duty to make any payment for the Clinical Trial Subjects recruited after the date of receipt of its notice.

(b) If recruitment of Clinical Trial Subjects is proceeding at a rate above that required to meet the relevant Timelines the Sponsor may with the

agreement of the Principal Investigator increase the number and amend the rate of Clinical Trial Subjects to be recruited and enrolled at the Trial Site;

6. QUALITY ASSURANCE AND CONTROL

6.1. The Site Parties shall permit the Trial Monitor and any Auditor access to all relevant clinical data of Clinical Trial Subjects for monitoring of the progress of the Clinical Trial, the proper collection and recording of Clinical Trial data, the welfare of the Clinical Trial Subjects, and altogether the good quality of the Clinical Trial and compliance with applicable Law and Sponsor's Standard Operating Procedures. The Trial Monitor's access will be arranged at mutually convenient times and on reasonable notice.

6.2. The Site Parties shall permit authorized representatives of the Ethics Committee and Competent Authorities to have access to, copy and verify information relating to the Clinical Trial, as required by and in accordance with applicable Law. Furthermore Sponsor acknowledges and agrees that the Institution executive management and local ethics committee will have the right to audit the performance of the Clinical Trial at the Trial Site.

6.3. In the event that the Sponsor reasonably believes there has been any research misconduct in relation to the Clinical Trial, Site Parties shall provide all reasonable assistance to any investigation into any alleged research misconduct undertaken by or on behalf of the Sponsor, the results of which the Party on whose behalf the investigation was undertaken shall, subject to any obligations of confidentiality, communicate to the Principal Investigator. In the event that the Principal Investigator reasonably believes there has been any research misconduct in relation to the Clinical Trial, the Sponsor shall provide all reasonable assistance to any investigation undertaken by or on behalf of the Principal Investigator, the results of which shall, subject to any obligations of confidentiality, be communicated to the Sponsor.

6.4. The Principal Investigator or the Institution shall promptly inform the Sponsor of any intended or actual inspection, written enquiry and/or visit to the Trial Site by any regulatory authority in connection with the Clinical Trial and forward to the Sponsor copies of any correspondence from any such regulatory authority relating to the Clinical Trial. The Site Parties shall allow Sponsor representatives to be present during any such visit.

6.5. The Site Parties will permit the Sponsor to examine the conduct of the Clinical Trial and the Trial Site upon reasonable advance notice and in the company of a Site Party's representative, during regular business hours to determine that the Clinical Trial is being conducted in accordance with the Protocol, this Agreement and applicable Law.

6.6. The Principal Investigator shall take appropriate measures and cause the Research Staff to take appropriate measures and corrective actions without delay as the Sponsor may reasonably require in order to solve all problems found and reported

by the Trial Monitors and any of the aforesaid Auditors, or representatives of the Ethics Committee, Competent Authority or other regulatory authority.

6.7. It is expressly agreed between the Parties that (a) the Sponsor will not compensate the Principal Investigator nor any member of the Research Staff for the assistance or guidance of representatives of the Ethics Committee, Competent Authority or other regulatory authority and (b) the assistance or guidance of Trial Monitors or Sponsor's auditors by the Principal Investigator and the Research Staff shall be deemed included in the remuneration paid pursuant to clause 12 hereinafter unless expressly agreed otherwise in writing.

6.8. The Principal Investigator shall submit CRF/eCRFs to the Sponsor. If needed, Sponsor will provide the Principal Investigator with a computer and or internet connection in order to submit e-CRFs for the Clinical Trial.

6.9. The Principal Investigator and any member of the Research Staff will be trained by Sponsor with respect to the use of eCRFs. Before the training process, the Principal Investigator and each member of the Research Staff shall sign an acknowledgment agreement which shall contain statements of understanding and acceptance of their obligations regarding the eCRF process.

6.10. The Principal Investigator shall ensure that all procedures defined in the Protocol are complied with, so that all data generated at the Trial Site are reliable and have been processed correctly (especially the randomization lists, and the blind character of the Clinical Trial as the case may be) and will ensure that the content of the case report form (CRF) /electronic case report form (e-CRF) will accurately reflect source documents.

7. INVESTIGATIONAL PRODUCTS

7.1. Parties acknowledge and agree that the Institution's pharmacist, or such other pharmacist as appointed by Sponsor the Principal Investigator and the Institution, will be responsible for certain tasks in relation with the handling of the Investigational Product. Any agreements between the pharmacist and any of the Parties will be in writing and must be in accordance with the Institution's internal policies. Any such agreements will be annexed to this Agreement as Annex 4.

7.2. Subject to the foregoing, the Sponsor will provide the Principal Investigator and the pharmacist with all necessary information on the Investigational Product(s), quality and handling instructions thereof and sufficient quantities needed to conduct the Clinical Trial.

7.3. The Principal Investigator shall not use or permit the Research Staff or any third party to use the Investigational Product for any purpose other than the conduct of the Clinical Trial and upon termination or expiration of this Agreement all unused Investigational Product shall, at the Sponsor's option, either be returned to the Sponsor or disposed of in accordance with the Protocol or the Sponsor's written instructions.

7.4. In case Sponsor has provided any equipment, such equipment to be further described in Annex 5 attached to this Agreement, to Institution or the Principal

Investigator for the conduct of the Clinical Trial at the Trial Site, such equipment shall remain the property of Sponsor and shall be treated in accordance with the provisions as described in more detail in said Annex 5.

8. CONFIDENTIALITY

Medical Confidentiality and Samples

8.1. It is the responsibility of each Party to effect and maintain all registrations for the processing of Clinical Data as required by the Dutch privacy law and legislation. Each Party shall be responsible for its own processing of personal data in accordance with all law and regulations and with the informed consents obtained from Clinical Trial Subjects.

8.2. The Parties agree to adhere to the principles of medical confidentiality in relation to Clinical Trial Subjects.

8.3. As part of the Protocol, Samples may be transferred to Sponsor or another organization indicated by Sponsor. Sponsor warrants, that the Samples are collected solely for the purpose of the Clinical Trial in accordance with the Protocol, the informed consent form obtained from the Clinical Trial Subject and in compliance with Dutch applicable Law and that the Samples shall not be used for any other purpose.

8.4. Sponsor acknowledges that Clinical Trial Subjects – and/or their legal representatives on their behalf – may withdraw or change their initial informed consent. Principal Investigator shall promptly notify Sponsor of any withdrawal of or changes in the informed consent of a Clinical Trial Subject, which may affect the use of such Clinical Trial Subject's Samples under this Agreement. Sponsor shall follow the instructions of the Principal Investigator in the handling and/or disposal of the respective Samples.

8.5. Sponsor shall refrain from tracing and/or identifying any Clinical Trial Subject. In the event any Clinical Trial Subject, for whatever reason, becomes identifiable to Sponsor, Sponsor agrees to preserve, at all times, the confidentiality of information pertaining to such Clinical Trial Subjects. Sponsor shall adopt appropriate technical and organizational measures to prevent any unauthorized or accidental use, access or processing of clinical data and/or Samples (Security Breach). Security Breaches shall be reported to the Principal Investigator promptly.

8.6. Upon termination or expiration of the Clinical Trial, and at least at any time the Samples are no longer needed to be retained by Sponsor for any pending registration purpose related to the Investigational Product in relation to the Protocol or to be retained in accordance with any applicable law or regulation, the remainder of the Samples in Sponsor's or any of its designee's possession will be destroyed by Sponsor.

Confidential Information

8.7. The Receiving Party shall ensure that only those of its officers and employees (and those of its Affiliates and members of the Research Staff) and Agents directly concerned with the carrying out of this Agreement have access to the Confidential Information of the Disclosing Party. The Receiving Party shall take all practicable steps to ensure that such persons abide by the same obligations of confidentiality as apply to the Receiving Party under this Agreement. The Receiving Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the Disclosing Party, except where disclosure is required by a regulatory authority or by law, in which case the Receiving Party shall inform the Disclosing Party of such requirement and the information to be disclosed. Notification will be within a reasonable time prior to being required to make the disclosure or if such time is not available, immediately upon becoming known of the requirement to disclose, Confidential Information. The Receiving Party undertakes not to make use of any Confidential Information of the Disclosing Party, other than in accordance with this Agreement, without the prior written consent of the Disclosing Party.

8.8. The obligations of confidentiality and non-use set out in clause 8.7 shall not apply to information which:

a. is or becomes part of the public domain by any other means than a wrongful act or breach of this Agreement by the Receiving Party;
b. was or becomes in the Receiving Parties' lawful possession prior to the disclosure without restriction on disclosure;
c. has been independently developed by the Receiving Party without the use of Confidential Information of the Disclosing Party;
d. has been obtained by the Receiving Party from a third party who is not subject to a duty of confidentiality; or
e. is published in accordance with clause 11 hereof.

9. INTELLECTUAL PROPERTY

9.1. All Intellectual Property Rights and Know How owned by or licensed to any of the Parties prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Clinical Trial are and shall remain the property of that Party.

9.2. The Sponsor shall own the Intellectual Property Rights and Know How arising from and directly relating to the Clinical Trial, the Investigational Product (including but not limited to its formulation and use alone or in combination with other drugs) or the Protocol, but excluding any clinical procedure and improvements thereto that are clinical procedures of the Principal Investigator or of the Trial Site owner or lessee.

9.3. The Principal Investigator will promptly inform and cause the Research Staff to promptly inform the Sponsor of any invention or discovery arising from and directly relating to the Clinical Trial, the Investigational Product (including but not limited to its formulation and use alone or in combination with other drugs) or

the Protocol, and hereby assigns all assignable rights in relation to all Intellectual Property Rights, and will provide reasonable assistance to the Sponsor in filing or prosecuting Intellectual Property Rights, at the expense of the Sponsor.

9.4. Nothing in this clause 9 shall be construed so as to prevent or hinder the Institution or the Principal Investigator from using the Know How generated in the Clinical Trial for its normal hospital and research activities to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Rights of the Sponsor.

10. PUBLICITY

The Sponsor will not use the logo or name of the Institution, Principal Investigator, nor of any member of the Research Staff, for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Principal Investigator, such approval not to be unreasonably withheld. The Site Parties will not, and will ensure that the Research Staff will not, use the name or logo of the Sponsor or of any of its employees, nor the name of the Clinical Trial, nor the name of the Investigational Product, for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Sponsor, such approval not to be unreasonably withheld.

Principal Investigator understands and agrees that his/her personal information including name, contact details, financial information relating to, among other matters, compensation and reimbursement payments for study conduct, and other personal data of the Principal investigator in connection with Principal Investigator's conduct of the Clinical Trial will be processed both by computer and manually, by Sponsor and its Affiliates and Agents in order to comply with Sponsor's and its Affiliates' obligations imposed by law, guidance or regulatory authorities and for considering from time to time potential investigators for future studies or organizing safety reporting. Principal Investigator further understands and agrees that his/her personal data may, if necessary for these purposes, be made available to regulatory authorities and ethics committees. Principal Investigator understands and agrees that the Sponsor’s use and disclosure of his/her personal data may involve use and disclosure in countries other than that where the Principal Investigator is located. Such countries may include but not be limited to: the United States, Japan, Canada, Australia, New Zealand, Switzerland, or countries in Latin America or Asia. Principal Investigator further understands that not all countries to which personal information may be transferred offer an equivalent level of protection of privacy of personal information. Principal Investigator is entitled to his/her personal data held by Sponsor or its Affiliates upon request and to have such data corrected if necessary.

11. PUBLICATION AND AUTHORSHIP

11.1. The Sponsor acknowledges the importance of public disclosure/publication of information collected or generated by the Principal Investigator, under the condition that public disclosure/publication takes place under the provisions of this clause 11.

11.2. Upon completion of the Clinical Trial (whether prematurely or otherwise) the Principal Investigator and Sponsor shall co-operate in producing a report of the Clinical Trial detailing the methodology, results and containing an analysis of the results and drawing appropriate conclusions.

11.3. The Sponsor agrees that the Principal Investigator shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of its own choosing, methods and results of the Clinical Trial, subject to this clause 11 and any publication policy described in the Protocol, provided any such policy does not obstruct publication unreasonably.

11.4. Upon completion of the Clinical Trial, or when the Clinical Trial data are adequate (in Sponsor's reasonable judgement), and subject to clause 11.7 hereof, the Principal Investigator may prepare the data derived from the Clinical Trial for publication or presentation. Material for public dissemination will be submitted to the Sponsor for review at least forty-five (45) days (or the time limit specified in the Protocol if longer provided it shall not exceed the time limit given under clause 11.6 sub a) prior to submission for publication, public dissemination, or review by a publication committee.

11.5. The Principal Investigator agrees that all reasonable comments made by the Sponsor in relation to a proposed publication or presentation will be incorporated into the publication or presentation.

11.6. During the period for review of a proposed publication referred to in clause 11.4 above, the Sponsor shall be entitled to

a. make a reasoned request to the Principal Investigator that publication be delayed for a period of up to ninety (90) days from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information and/or Intellectual Property Rights and Know How and the Principal Investigator shall not unreasonably withhold its consent to such a request; and

b. may cause the Principal Investigator to remove from the projected publication any Sponsor Confidential Information received by Principal Investigator that are not constituted results of the Clinical Trail.

11.7. If it is a multi-centre Clinical Trial, any publication based on the results obtained at the Trial Site (or a group of sites) shall not be made before the first multi-centre publication or presentation unless otherwise agreed in writing, or as provided for in clause11.7 hereof. If a publication concerns the analyses of sub-sets of data from a multi-centred Clinical Trial the publication shall make reference to the relevant multi-centre publication(s). Notwithstanding the foregoing, if a multi-centre publication is not published within twelve (12) months after completion of

the Clinical Trial and lock of the Clinical Trial database at all research sites that are part of the multi-centre Clinical Trial or any earlier termination or abandonment of the Clinical Trial, the Principal Investigator shall have the right to publish or present the methods and results of the Clinical Trial in accordance with the provisions of this clause 11. The foregoing provided however, that any such publication will take in account the rights and interests of all investigators involved in the multi-centre Clinical Trial and authorship will be determined in accordance with clause 11.8.

11.8. Publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, established by the International Committee of Medical Journal Editors. Copyrights concerning Publications of the Clinical Trial remains with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.

11.9. The Principal Investigator will not issue and will cause the Research Staff not to issue any information or statement to the press or public, including but not limited to advertisements for the enrolment of Clinical Trial Subjects, without, where appropriate, its review and the delivery of a favourable opinion from the Ethics Committee and the prior written permission of the Sponsor.

12. TERM AND TERMINATION

12.1 This Agreement commences on the Effective Date and shall continue in force until the earlier of:

a. completion of the Clinical Trial, close-out of the Trial Site and completion of the obligations of the Parties under this Agreement; or

b. early termination in accordance with clauses 12.2, 12.3 or 12.5 of this Agreement;

12.2 Each Party may terminate this Agreement upon written notice to the other Parties with immediate effect in the following events:

a. if the approval by the Ethics Committee in charge of the Clinical Trial is irrevocably revoked;

b. if it can be reasonably assumed that the Clinical Trial must be terminated in the interests of the health of the Clinical Trial Subjects;

c. If it becomes apparent, following confirmation of the Ethics Committee or the DSMB, that continuation of the Clinical Trial cannot serve a scientific purpose, and this is notified to the Ethics Committee;

d. if the Sponsor and/or the Institution and/or the Principal Investigator become or are declared insolvent or a petition in bankruptcy has been filed against it or if one of them is dissolved;

e. if circumstances beyond a Party's control occur that render continuation of the Clinical Trial unreasonable;

f. if one of the parties fails to comply with the obligations arising from the Agreement and, if capable of remedy, is not remedied within 30 days after receipt of notice from the other Party specifying the non compliance and

requiring its remedy, unless failure to comply is not in reasonable proportion to the premature termination of the Clinical Trial.

12.3 Either Party may terminate this Agreement if the Principal Investigator is no longer able (for whatever reason) to act as Principal Investigator and no mutually acceptable replacement has been found in accordance with clause 2.3.

12.4 In all circumstances causing the early termination of this Agreement pursuant to clauses 12.2 or 12.3 above, the Sponsor shall confer with the Principal Investigator and use their best endeavours to minimise any inconvenience or harm to Clinical Trial Subjects caused by the premature termination of the Clinical Trial.

12.5 Sponsor may terminate this Agreement upon written notification to the Principal Investigator and the Institution, with immediate effect, in the following events:

a. for lack of recruitment at the Trial Site in case the Clinical Trial is conducted at one Site only; or

b. in case of a multicentre trial, if termination at the Trial Site does not affect performance of the Protocol.

The foregoing provided however, that this clause 12.5 shall not apply and Sponsor shall have no right to terminate this Agreement if any Clinical Trial Subject has undergone treatments or conduct has been imposed on the Clinical Trial Subject as per the Protocol, at the Trial Site.

12.6 If the Agreement is terminated by the Sponsor for one of the reasons in clauses, 12.2, 12.3 or 12.5, except for material breach by the Institution and/or the Principal Investigator under clause 12.2 (f), and subject to an obligation on the Institution and the Principal Investigator to mitigate any loss, the Sponsor shall pay all fees and expenditures falling due for payment by the Principal Investigator and/or the Institution up to the date of termination, and also all expenditure falling due for payment after the date of termination which arises from commitments reasonably and necessarily incurred by the Principal Investigator and/or Institution for the performance of the Clinical Trial prior to the date of termination, and agreed with the Sponsor and which cannot be cancelled. In case the Agreement is terminated by the Institution and/or the Principal Investigator for one of the reasons in clauses 12.2 or 12.3, Sponsor will in principle compensate Institution and/or Principal Investigator for fees and expenditures falling due for payment by the Institution and/or Principal Investigator up to the date of termination, except for material breach by the Institution or the Principal Investigator under clause 12.2 (f) and provided the occurrence of such reasons is beyond the control or influence of Institution and/or Principal Investigator.

12.7 In the event of early termination if payment (whether for salaries or otherwise) has been made by the Sponsor to the Institution or the Principal Investigator in advance for work not completed, such monies shall be applied to termination related costs and the Institution and/or the Principal Investigator shall issue a credit note and repay the remainder of the monies within 45 days of receipt of written notice from the Sponsor.

12.8 At close-out of the Trial Site following termination or expiration of this Agreement the Principal Investigator and the Institution shall immediately deliver to the Sponsor all Confidential Information and any equipment pursuant to the terms and conditions of Annex 5 provided to the Institution and/or the Principal Investigator pursuant to this Agreement.

12.9 Termination of this Agreement will be without prejudice to the accrued rights and liabilities of the Parties under this Agreement.

13. FINANCIAL PROVISIONS

13.1. The Sponsor will provide funding in support of the Clinical Trial as set out in Annex 3.

13.2. In the event that amendments to the Protocol require changes to the Clinical Trial financing arrangements, such amendments will be subject to a written agreement between the Sponsor and the Principal Investigator

13.3. All payments, including VAT will be made according to Annex 3 upon receipt of an invoice from or on behalf of the Principal Investigator. All payments will be made within the timeframe stated in the invoice

13.4. For the avoidance of doubt, the sums paid pursuant to this clause 13 to the Principal Investigator shall be an all-inclusive remuneration for the performance of the Clinical Trial carried out at the Trial Site.

14. MISCONDUCT AND DEBARMENT

14.1 The Principal Investigator represents and warrants that neither he/she nor any collaborator of the Principal Investigator involved in conducting the Clinical Trial nor any member of the Research Staff, has been debarred, excluded, disqualified or restricted in their ability to practice medicine, participate in a clinical trial, or perform services in connection with the evaluation of a pharmaceutical product under any laws, regulations or professional code of conduct including without limitation United States Code of Federal Regulations ("U.S.C." or "CFR") title 21 section §335a and section §312.70.

14.2 The Principal Investigator shall immediately notify Sponsor should he/she or any collaborators or any member of the Research Staff involved in conducting the Clinical Trial, be so debarred, excluded, disqualified or restricted, or should a procedure or action be initiated against any of them that could result in their being so debarred, excluded, disqualified or restricted, at any time during the term of this Agreement and during the twelve months following the expiration or termination of the Agreement.

15. DISCLOSURE OF FINANCIAL INTEREST

15.1 Principal Investigator shall ensure that he/she and collaborators and any member of the Research Staff involved in this Clinical Trial at Principal Investigator's Clinical Trial Site provide Sponsor with the appropriate financial disclosures required for compliance with CFR title 21 Part 54, on such forms as Sponsor may supply or approve.

15.2 During the term of this Agreement and for one (1) year following termination or completion of the Clinical Trial, Principal Investigator shall promptly notify Sponsor of any material change in the information disclosed on a previous form.

16. FORCE MAJEURE

16.1 No Party shall be liable to the other Parties or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, and epidemic or because of any other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Parties in writing when such circumstances cause a delay or failure in performance and where they cease to do so.

17. RELATIONSHIP BETWEEN THE PARTIES

17.1. No Party may assign its rights under this Agreement or any part thereof without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed, and no Party may sub-contract the performance of all or any of its obligations under this Agreement without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed. Any Party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.

17.2. Nothing shall be construed as creating a joint venture, partnership or contract of employment between the Parties.

17.3. Should there be a conflict between the terms and conditions of the Protocol and the Agreement concerning clinical matters, the Protocol shall prevail.

17.4. Unless otherwise agreed, notices to the respective Parties shall be given, made or served if in writing and delivered personally or send by overnight carrier or by facsimile with receipts confirmed as follows:

If to Sponsor:
[insert full contact details]
If to Institution:
[insert full contact details]
If to Principal Investigator:
[insert full contact details]

18. SURVIVAL OF CLAUSES

The clauses 4; 7.3; 8; 9; 10; 11; 12.4; 12.5; 12.6; 12.7; 14; 15; 16; 17; 18 and 19 shall survive termination of this Agreement. The provisions of clause 8.7 shall remain in force for a period of ten (10) years after the termination or expiry of this Agreement.

19. GOVERNING LAW AND DISPUTE RESOLUTION

This Agreement shall be governed by, and construed in all respects in accordance with the laws of The Netherlands without regard to its conflicts of laws rules. Any claims, controversies or disputes arising out of or in connection with this Agreement which cannot be settled amicably between the Parties, shall be subject to the exclusive jurisdiction of the competent court of Amsterdam.

Annexes

Annex 1: Protocol
Annex 2: Timelines
Annex 3: Financial arrangements
Annex 4: Pharmacist agreement
Annex 5: Equipment
Annex 6: Bribery and Corruption Statement

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Signed on behalf of the **Sponsor**

Signature: ……
Name: ……
Title: ……

Date: ……

Signed on behalf of the **Institution**

Signature: ……
Name: ……
Title: ……

Date: ……

Signed by the **Principal Investigator**

Signature: ……
Name: ……
Title: ……

Date: ……

ANNEX 1

PROTOCOL

ANNEX 2

TIMELINES

ANNEX 3

FINANCIAL ARRANGEMENTS

ANNEX 4

PHARMACIST AGREEMENT

ANNEX 5

EQUIPMENT

ANNEX 6

Bribery and Corruption

(A) The Trial Parties must at all times act with integrity and honesty and comply with the highest ethical standards.

(B) The Trial Parties must not make, give, or offer any payment, gift or other benefit or advantage to any person for the purposes of:

(i) securing any improper advantage; or

(ii) inducing the recipient or another person to do or omit to do any act in violation of their duties or responsibilities (or for the purposes of rewarding such conduct).

This restriction applies at all times and in all contexts. For the avoidance of any doubt, it applies both to dealings with "public officials" and to dealings with employees and agents of commercial enterprises.

(C) Nevertheless, particular care must be exercised with dealings with public officials. The Trial Parties must not make, give or offer any payment, gift or other benefit or advantage for the purposes of influencing any act or decision of a public official (or inducing such official to use their influence with another person, entity or government instrumentality or to affect or influence any act or decision of such other person, entity or government instrumentality).

(D) The term "***Public Official***" includes any person acting on behalf of any government department, agency or instrumentality or any state-owned or controlled enterprise. By way of example, this includes health care professionals employed by a state- or local municipality-run hospital or clinic, and representatives of public international organizations.

(E) The Trial Parties must not make, give or offer any payment, gift or other benefit or advantage to any person whilst knowing or suspecting that all or a portion of such money, gift, benefit or advantage will be used, whether directly or indirectly, in breach of (B) or (C) above.

(F) The Trial Parties shall make and keep books, records, and accounts, which, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the Trial Parties.

(G) The Trial Parties shall devise and maintain a system of internal accounting controls sufficient to provide reasonable assurances that –

(i) transactions are executed in accordance with management's general or specific authorization;

(ii) transactions are recorded as necessary

(I) to permit preparation of financial statements in conformity with generally accepted accounting principles or any other criteria applicable to such statements, and

(II) to maintain accountability for assets;

(iii) access to assets is permitted only in accordance with management's general or specific

authorization; and

(iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences.