Clinical study agreement

Name of the study: Prevalence, diagnosis, management and outcome of mesenteric ischemia: a prospective, observational multicenter study (AMESI Study) (hereinafter: study)

PARTIES to the agreement
Sponsor:
Name: University of Tartu,
[redacted]
Representing person: Pille Taba, Head of the Institute of Clinical Medicine

Institution: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla
Name: **Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla**
[redacted]
Representing person: José Cañón Campos. Managing Director

1. SCOPE OF THE AGREEMENT

Under this agreement, the parties agree to conduct a clinical study as defined in the Protocol in Appendix 1 **AMESI Study,** as may be amended from time to time. The study is part of the project "Acute mesenteric ischemia: development of an algorithm for diagnosis and management" (PRG1255) funded by the Estonian Research Council.

2. PURPOSE OF THE AGREEMENT

The purpose of this agreement is to agree on terms and conditions, as well as procedures, according to which the study will be conducted, and on the division of duties and responsibilities between the parties conducting the study.

3. CONTACT PERSONS

Contact person(s) for the Sponsor:
[redacted]

Contact person(s) for the Institution:
[redacted]

4. TIMELINE and SCHEDULE OF THE STUDY

4.1. This clinical study can only be initiated after full approval by the local ethics committee at the study site (Institution) has been obtained.

4.2. The purpose of the study is to screen Institutional patients and to enrol appropriate patients with Acute Mesenteric Ischaemia (AMI) during the study period. On suspected cases, only basic data is collected; no reimbursement is provided. For confirmed cases, a full data set is collected and recruitment will be reimbursed by the Sponsor.

4.3. The global target is to enrol at least 400 patients with confirmed AMI by 31.12.2022. The objective for the **Institution** is to be ready to commence recruitment in May 2022 (the earliest study start date is 16.05.2022) and recruit the first subject into the study by 30.09.2022. The Sponsor of the study is, however, entitled to suspend the recruitment of new subjects if a sufficient number of subjects has been recruited into the study globally at the interim analysis time point four months after the study start.

[redacted]

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- The study is regarded completed when the Sponsor has received the data collected or generated in accordance with the protocol, and given its approval and informed the Institution thereof. The estimated total duration of the study including the 1-year follow-up period is from May 2022 to December 2023.

- **BACKGROUND MATERIAL AND RIGHTS OF USE**

The Sponsor shall provide the Institution with the data and documents required for conducting the study. The data and documents provided by the Sponsor may be used solely for the conduct of this study in accordance with the current agreement.

- **LEGISLATION AND GUIDELINES ON CONDUCTING THE STUDY**

The following legislation and regulations shall be complied with in the conduct of the study:

- Valid legislation, regulations and guidelines of the authorities from the side of Sponsor and Institution;
- Guideline for Good Clinical Practice (ICH GCP), latest version;
- The principles of the (World Medical Association) Declaration of Helsinki, latest version.

- **LIABILITIES AND RESPONSIBILITIES OF THE PARTIES**

- In addition to the other liabilities and responsibilities described in this agreement, the Institution is obliged to:
  - act as the employer of the investigators conducting the study;
  - allow participation of the investigators and when appropriate/necessary also study nurses in investigator meetings and other education arranged by the Sponsor;
  - ensure that the investigators are familiar with the details of the protocol and other liabilities and responsibilities defined in this agreement, and that investigators are committed to act accordingly;
- In addition to the other liabilities and responsibilities described in this agreement, the Sponsor of the study is obliged to:
  - provide the Institution with the necessary background information needed for the appropriate and safe conduct of the study;
  - ensure necessary preparation of the investigators of the Institution via web-meetings in order to conduct the study in accordance with the protocol;
  - inform the Institution of the completion of the study.

- **PRINCIPAL INVESTIGATOR AND HIS/HER RESPONSIBILITIES**

The principal investigator at the study site (Institution) will be:

[redacted]

- The principal investigator is obliged to:
  - follow all relevant legislation;
  - get fully acquainted with the protocol and all information and documents provided

by the Sponsor;

- conduct the study in accordance with the protocol as approved by the Ethics Committee including potential future approved amendments thereto;
- ensure that all the persons assisting in the study and also others engaging in the treatment of the subjects have been properly informed of the protocol;
- ensure protection of patients' personal data; patients' personal data will not be transferred outside the Institution;
- ensure accuracy, completeness, reliability, and timeliness of the information submitted to the Sponsor on the case report forms and in answering any queries;
- promptly complete all case report forms that are electronically located in the REDCap platform. Entering new patient in the database is requested within 20 days of inclusion of the patient, and entering all data for the hospital stay within 30 days after the subject has been discharged from hospital.

- **COMPENSATIONS, INVOICING AND PAYMENT**

- For each patient with confirmed AMI (see study protocol in Appendix 1) the Sponsor will reimburse the Institution 200 EUR (excluding VAT). Payments will be transferred from Sponsor to Institution after the recruitment phase of the investigation has been completed, provided the Institution's recruited patients in-hospital dataset is completed and entered into the REDCap electronic Case Report Form. The Institution is also responsible for follow-up data completion beyond the index admission.
- Invoicing address and the contact person of the Sponsor:

[redacted]

- Invoicing details

  In relation to the study, the following payment terms are followed: 30 days after issuing of a formal invoice by the Institution.

  The Institution shall be responsible for invoicing the costs (number of patients) from the Sponsor.
- The invoice must include the following details:
  - Name of the study: Prevalence, diagnosis, management and outcome of mesenteric ischemia: a prospective, observational multicenter study (AMESI Study);
  - Name of Institution;
  - Number of patients included for whom reimbursement is sought,
  - Indicating the patient's study ID and the date of inclusion.
- Any other invoices/payments (such as for ethics approval submission fees) need to be negotiated with the Sponsor on a case by case basis before any invoicing process.

- **CONFIDENTIALITY AND PERSONAL DATA PROTECTION**

- The Institution shall keep in confidence especially all information related to and accrued in connection with the study, the results, documents, and electronic records whether they are especially marked or not as confidential. All documents and electronic

records that contain confidential Information must be stored in a manner to which no third party may have access.

- For the avoidance of doubt, "personal data" are as defined in the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, (General Data Protection Regulation). Personal data shall always be treated as confidential, and shall be protected with an adequate level of safety and confidentiality, subject to any applicable legal, regulatory or contractual requirements. The Institution shall keep confidential the personal data of the subjects accrued in connection with the study.

- **DATA AND RESULTS ACCRUED IN CONNECTION WITH THE STUDY**

All information, documents, reports, materials and other results accrued in connection with this study (hereinafter "Results") apart from the patient records and other data collected by the Institution for its own use are the property of the Sponsor of the study, the use of which the Sponsor of the study may decide independently.

- **INTELLECTUAL PROPERTY RIGHTS**

All copyrights and other intellectual property rights generated as a result of this study are the property of the Sponsor of the study.

- **PUBLICATION OF RESULTS**

- In this multi-centre study, no results concerning the study may be published prior to the receipt and analysis of the study results from all study centres.
- The Institution and/or Investigator will not disclose or publish any results of the study until results from all sites participating in the study have been received, analysed and published by the Sponsor.
- The principal investigator of the entire multi-centre study shall be responsible for the publication of the study results.
- Each party shall follow Authorship Rules as defined in Appendix 2.
- Upon termination of the study, the investigator has the right to independently analyse his/her own study results and publish them. The Sponsor shall obtain the manuscript of the publication for its assessment thirty (30) days prior to it being submitted for publication.

- **AMENDMENTS**

All changes and amendments to this agreement shall be agreed in writing between the parties.

- **ENSURING CONDUCT OF THE STUDY**

The Institution shall be responsible for ensuring sufficient and appropriate resources for the conduct of the study.

- **FORCE MAJEURE**

Any event occurring after signing the agreement, which a party could not reasonably have considered at the time of the conclusion of the agreement and which prevents or delays the affected party from fulfilling its obligations under the agreement or makes the fulfilment thereof unreasonably difficult and which can not be overcome without unreasonable loss of time or cost, shall constitute an event of force majeure. An event of force majeure shall

include: strike, war, revolt, import or export prohibition, acts of God, interruption of public traffic or distribution of energy, legal labour dispute, fire or any other reason having severe and unusual effects beyond the control of the party.
If a party would wish to invoke existence of an event of force majeure as a cause for the non-compliance with any of its obligations under the agreement or delay or exemption from liability, it shall without delay inform the other party of the delay or termination of its contractual obligation in writing.

- **RETENTION AND DESTRUCTION OF STUDY RECORDS**

The Institution shall store any original study documents on site according to the applicable regulations and law. Patients' personal data will not be transferred outside the Institution; only pseudonymized data will be entered in the electronic Case Report Form (REDCap).

- **TRANSPARENCY**

The Investigator shall declare, according to the instructions from the Sponsor, that the Sponsor has provided her/him with funding for the study whenever she/he writes or speaks in public about a matter that is the subject of this agreement or about any other issue relating to the Sponsor.

- **COMPLAINTS AND LIABILITIES**

Each party is obliged to notify the other party immediately in writing of all errors, omissions, and deficiencies detected in the conduct of the other party as based on this agreement. Thereafter, the defaulting party has a duty to correct the reported error, omission, or deficiency.

- **TERM AND TERMINATION OF THE AGREEMENT**

- This agreement shall become effective upon signing by both parties. The agreement shall continue in effect until 29.02.2024 or until both parties have fulfilled their obligations as set forth by this agreement.
- Without prejudice to the term of the agreement, a party may terminate this agreement with immediate effect, if:
  - the other party is in material default of any of its obligations under this agreement and the breach is of significant importance to the other party;
  - the other party fails to comply with its obligations under this agreement and has not corrected its default, omission, or deficiency within four (4) weeks after the non-defaulting party has given the defaulting party written notice thereof.
- The principal investigator, the Institution, or the Sponsor has the right to suspend the conduct of the study and serve notice of termination with immediate effect due to any cause relating to the safety of the subjects or any ethical reason, including if a favourable opinion of the Ethics Committee is not obtained.
- In case of a systematic error or deviation from the protocol (e.g. inclusion of inappropriate patients) that has not been corrected during 30 days after respective notice with at least one reminder, the Sponsor shall in addition have the right without separate obligation of compensation or refund to suspend the Institution from the study and terminate this agreement.

- **MISCELLANEOUS**

- This agreement shall be governed by the laws of Estonia.
- Nothing in this agreement shall create or be deemed to create a partnership or to have

created the relationship of principal and agent, a membership or any other legal entity between the parties.

- The Institution may not sub-license, assign, transfer, mortgage or part with this agreement or any of its rights, duties or obligations under this agreement without prior written consent from the Sponsor.
- This agreement, including its appendices, represents the entire understanding between the parties with respect to the conduct of the study and supersedes all prior oral or written agreements between the parties related thereto.

SIGNATURES

This agreement has been made in two (2) copies, one for each party.

Sponsor: University of Tartu

Institution: Hospital Universitario Virgen del Rocio. Unidad de Cirugía de Urgencias.

Principal investigator at the study site: Virginia Durán Muñoz-Cruzado