** AID-ICU**

**Clinical Trial Agreement**

This Clinical Trial Agreement (“Agreement”), dated as of last signature (“Effective Date”) is made by and between;

**Sponsor:**

 Zealand University Hospital, Køge

 Lone Musaeus Poulsen

 Department of Anaesthesiology and Intensive Care

 Lykkebækvej 1, 4600 Køge, Denmark

 (hereinafter called "Sponsor")

**and**

**Institution:**

 [INSERT]

 [INSERT]

 [INSERT]

 Company no.: [INSERT]

 (hereinafter called “Institution”)

**Represented by**

 [INSERT name]

 [INSERT title]

 (hereinafter called”Investigator”)

Dr. [INSERT]*, an employee of Institution* will be responsible for the performance of the Study on behalf of the Institution

The Institution and Sponsor are hereinafter each individually referred to as a “Party” and collectively referred to as the “Parties”.

#### Preamble

#### WHEREAS Sponsor is the Sponsor (as that term is defined by the European Clinical Trials Directive (Directive 2001/20/EC) (hereinafter referred to as “EU CTD”), and any other applicable laws and regulations governing clinical trials) for this Study and shall assume all applicable Sponsor responsibilities in any country where the Study is conducted. Under no circumstances shall the Institution or the Investigator be deemed the Sponsor of this Study, as that term is defined under applicable laws and regulations. Sponsor is the Sponsor of the clinical multi-centre study regarding Haloperidol, (hereinafter defined as “the Study Drug”) as defined in the protocol entitled Agents Intervening against Delirium in the Intensive Care Unit, , a copy of which is incorporated herein by reference as Appendix A, (hereinafter defined as “the Study”) and wishes to enter into an agreement with Institution; and has requested Investigator to conduct the Study according to this Agreement and it’s Appendices, the Protocol including subsequent Protocol amendments.

WHEREAS, Investigator is equipped and authorized to undertake the Study and Investigator have agreed to perform the Study on the terms and conditions hereinafter set forth.

NOW THEREFORE in consideration of the premises and the mutual promises and covenants expressed herein, the Parties agree as follows:

**1. Obligations of the Parties**

* 1. **Authorizations**
		1. It is the responsibility of the Institution that the Study has been approved by the national competent authorities before trial initiation. The Sponsor shall where possible and relevant provide the Institution/Investigator with relevant documents required for submission to the Ethic Committee (EC) and competent authority except those which are specific of the Country and/or the trial site.
		2. In the event that EC requires amendments in the Protocol or informed consent form, such amendments shall be agreed upon by both the Institution/Investigator and Sponsor and be documented in writing.
		3. The Study can start only after a favourable opinion of the competent ethics committee and the approval of the competent medicines authority and any other required approvals have been obtained in accordance with the applicable law and the Institution’s standard policies.

**1.2 Conduct of Study**

1.2.1 The Parties shall conduct the Study in accordance with the Protocol and its amendments, the terms of this Agreement, and the terms and conditions of the approval of relevant authorities. Institution/Investigator shall adhere to separate manuals and specific procedures provided by Sponsorapplicable for conducting the Study.

1.2.2 Institution/Investigator shall be fully informed of the Protocol and the Study Drug. Sponsor shall provide all relevant clinical pharmacology and toxicology information and advice to Institution/Investigator, which are required for the proper planning and conduct of the Study. Such information will include the Investigator's Brochure (IB) and information on Suspected Unexpected Serious Adverse Events (SUSARs) for unlicensed products or the Summary of Product Characteristics (SPC) for licensed products. Investigator shall attend, or ensure a delegate attends, all Investigators’ meetings for the Study from time to time as reasonably required by Sponsor.

1.2.3 Institution/Investigator shall ensure that all the Institution's employees and collaborators, who are involved in the Study fully, understand and adhere to the Protocol and the obligations of both the Institution and the Investigator.

1.3 Data and Safety Reporting

1.3.1 Institution/Investigator shall on request submit written reports, in accordance with all laws, regulations and guidelines including the Ethics Committee standards, to Sponsor and the EC regarding the Study being conducted at the Institution.

1.3.2 Required Systems: Institution/Investigator agrees to implement and use any electronic system that Sponsor may specify for use in the reporting and monitoring of the Study and Study findings at Sponsor’s expense.

1.3.3 Investigator agrees to report to Sponsor immediately but not later than twenty-four (24) hours after learning of any serious adverse events and other important medical events, as identified in the Protocol, affecting any Study subject in the Study. Investigator further agrees to follow up such report with detailed, written reports in compliance with all applicable legal and regulatory requirements. Investigator shall record and evaluate all Adverse Events experienced by the Study subjects in accordance with the Protocol.

1.4 Record Management

1.4.1 Institution/Investigator will retain in a safe and secure location, one (1) copy of all printed and electronic data and reports resulting from the Study for the period as required by law or any regulatory requirements.

1.4.2 Institution/Investigator shall maintain accurate data collection and up-to-date records of all Study subjects.

**1.5 Study Drug and Equipment**

1.5.1 Sponsor shall provide free of charge, or as appropriate, reimburse Institution for materials that Sponsor is required to provide per the Protocol including Study Drug necessary for the conduct of the Study. Institution/Investigator shall not use the Study Drug for any purpose other than the conduct of the Study.

1.5.2 Institution/Investigator shall ensure that the Study Drugs are handled correctly and stored securely for the duration of the Study and any period thereafter as required by applicable law or this Agreement, whichever is later, in accordance with the Protocol. Only those persons who are under the Investigator's direct control and who will be using the Study Drug shall have access to the Study Drug.

1.5.3 Upon termination or completion of the Study, all unused Study Drug shall be at Sponsor's sole option and at Sponsor’s expense, destroyed.

**1.6. Informed Consent**

1.6.1 Investigator undertakes to provide patient information sheet(s) as approved by the national Ethics Committee in any language requested, and to obtain written informed consent according to national guidelines and regulations from each Study subject prior to inclusion or initiation of any Study specific procedures for screening according to the Protocol.

**1.7 Study subject Enrolment**

1.7.1 Institution/Investigator shall make reasonable efforts to ensure that the overall recruitment target of eligible subjects in accordance with the Protocol is meet timely and that data from all eligible Study subjects are available on or before the expiration of the Study.

1.7.2 As the Study is part of a multi-centre trial, Institution/Investigator may enrol Study subjects in mutual competition with other participating sites. Sponsor reserves the right to end Study subject enrolment under this Agreement when the desired number of Study subjects for all sites has been reached. Further, Institution and Investigator agree that continued screening or randomisation of subjects must not take place after Study Subject enrolment has been ended by Sponsor and notice hereof has been given to Institution by Sponsor.

**1. 8 Monitoring and Audit**

1.8.1 Sponsor shall provide reasonable supervision, training and monitoring during the conduct of the Study.

1.8.2 Institution/Investigator shall during the Study, on reasonable prior written notice and at an agreed upon time, permit authorized personnel of Sponsor to access the site during normal business hours in order to conduct monitoring and audits.Any review by Sponsor of source documents shall be performed with due regard for Study subject confidentiality.

1.8.3 Institution/Investigator is obliged throughout the trial to keep local printed documents in the Site Master File up to date using the trial websites log for such updates.

**2. Compensation**

2.1 The budget and compensation to be paid for the Study are included in Appendix B. Payment shall be due and payable in accordance with the schedule and details set forth in Appendix B.

2.2 The Parties acknowledge and agree that the compensation and support provided by Sponsor to Institution pursuant to this Agreement has been negotiated in an arms-length transaction, and has not been determined in a manner that takes into account the volume or value of any referrals or other business otherwise generated between Sponsor and Institution.

2.3 Changes to the Protocol: In the event of a change to the Study Protocol that results in an increased cost, or if any increase in the compensation due for the conduct of the Study is necessary or appropriate, the Parties can negotiate further remuneration.

**3. Confidentiality**

3.1 All information furnished by both Parties (“Confidential Information”) pursuant to this Agreement, to Sponsor, Institution/Investigator, shall be treated by Sponsor and Institution/Investigator as confidential for a period of five (5) years after termination of this Agreement. Sponsor and Institution/Investigator shall i) hold the Confidential Information in confidence and not disclose or permit it to be made available to any third party, without the other Party’s prior written consent, ii) only use the Confidential Information for the Study, iii) take any reasonable steps to the effect that each person employed at the Sponsor or Institution to whom disclosure of the Confidential Information is made will be under the same confidentiality obligations as applies for Sponsor or Institution under this Agreement, and iv) upon written demand from Sponsor either at Sponsor’s expense to return the Confidential Information and any copies of it or to confirm in writing that it has been destroyed. However, Institution/Investigator may keep one copy for documentation purposes.

3.2 The foregoing Section 3.1 does not apply to any of the Confidential Information which Institution/Investigator can show i) is already lawfully known to Institution/Investigator at the date it was disclosed to it by Sponsor and is or becomes free of restriction on the disclosure or use in question, or ii) is or becomes generally known or freely available to the public (except by reason of any breach by Institution/Investigator of its obligations hereunder), or iii) is disclosed to Institution/Investigator, free of restriction on the disclosure or use in question, by a third party who was entitled to make such unrestricted disclosure, or iv) is independently developed by Institution/Investigator, or v) is disclosed, retained or maintained by law or any regulatory or government authority.

**4. Publication**

4.1 The Parties recognize that Danish law places an obligation on hospitals carrying out health and social care research to publish their work.

The Parties agree that this Section 4 should be interpreted in light of such obligation.

4.2 Following completion of the entire Study at all sites, Sponsor shall use all reasonable endeavors to ensure the appropriate publication or other dissemination of the conclusions of the Study, and Institution/Investigator for such Study shall not publish data/results derived from the individual institution site until the combined results from the entire Study has been published in a joint, multi-centre publication, cf. the Protocol. If such a multi-centre publication is not submitted within twelve (12) months after conclusion, abandonment or termination of the Study at all sites, or after the Sponsor confirms there will be no multi-centre clinical trial publication, Institution/Investigator may publish the data/results from the Institution individually in accordance with this Section 5.

4.3 Site investigators authorships and the order of authorship for the Sponsors team will be as described in the protocol.

4.4 If Institution/Investigator wish to publish data/results from the Study, a copy of the manuscript must be provided to the Sponsor for review at least thirty (30) days prior to submission for publication, presentation or release. The Sponsor and Investigator will arrange expedited reviews for abstracts, poster presentations or other materials. Within this 30 day period, the Sponsor shall review such proposed publication or presentation or release to determine whether it contains any Confidential Information of Sponsor (as defined in Section 3), or whether Sponsor desires to file patent applications on subject matter contained therein. Upon receiving any notification from Sponsor requesting deletion of Confidential Information of Sponsor, or requesting a delay in publication to allow the filing of patent applications before publication or release, Investigator shall take the requested action; provided however, that any delay in publication shall not exceed ninety (90) days from the date on which Sponsor received the draft manuscript for review.

**5. Publicity**

5.1 None of the Parties shall use the name of any other Party for marketing or promotional purposes without the prior written consent of the Party whose name is proposed to be used, nor shall either Party disclose the existence or substance of this Agreement except as required by law or otherwise provided for in this Agreement. Furthermore, Sponsor being a Danish public body is encompassed by the Act of Publicity within the Public Administration.

**6. Ownership of Data**

6.1 All data/results generated by Institution/Investigator in the direct course of conducting the Study (“Data”) shall be transferred to Sponsor, which may utilize the Data in any way it deems appropriate, subject to and in accordance with applicable privacy and security laws and regulations and the terms of this Agreement.

6.2 Institution/Investigator retain right to use own Data for further research, education and treatment purposes.

**7. Ownership of Inventions**

7.1 Any inventions/improvements within the field of research, as resulting directly from the Study shall be owned by Sponsor (“Inventions”). Sponsor shall be entitled to file in its own name relevant patent applications or in other ways protect the Inventions, and the said Inventions will become and remain the property of Sponsor solely.

7.2 Institution/Investigator shall promptly disclose and assign to Sponsor all Inventions generated by Institution/Investigator pursuant to this Agreement.

**8. Indemnification**

8.1 The parties agree that all procedures are standard treatments normally used in the hospitals for that kind of patients. The treatment techniques are standard techniques normally used in each individual hospital.

 The Sponsor shall compensate the Institution for the necessary medical expenses required to treat a Subject as a result of an adverse event and it shall indemnify the Institution and its personnel and hold them harmless of and against all claims by or on behalf of the Subjects for personal injury or death, to the extent an adverse event, personal injury or death was caused by any test or procedure performed in compliance with the Protocol and other requirements of this Agreement, to which the Subjects would not have been exposed but for their participation in the Study, and not caused by the Institution or any party within their control.

 Sponsor’s indemnification of the Indemnities shall not apply to any claim or proceeding pursuant to clause 8.1, and Sponsor shall not be liable:

a. to the extent that said adverse event, personal injury or death is caused by any of the Indemnitees’ failure to comply with this Agreement; or

b. to the extent that said personal injury (including death) is caused by gross negligence recklessness or willful conduct or misconduct of any of the Indemnitees,

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, 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.

8.2 The Institution shall indemnify the Sponsor and its personnel and hold them harmless of and against all claims by or on behalf of the Subjects for personal injury or death, to the extent caused by the Institution indemnitees or any party within their control through

- breach of this Agreement,

- failure to use reasonable medical judgment in the conduct of the Study, including the enrolment of Subjects for whom participation in the Study is medically appropriate,

- negligence or willful misconduct, or

- misuse of the investigational product.

8.3 The indemnified party shall

- inform the indemnifying party in writing of any indemnified claims without delay,

- allow the indemnifying party to take control over the defence and settlement of the claim,

- not compromise or settle the claim without the indemnifying party’s prior written consent,

- have the right to appoint its own counsel to participate in the defence of the claim, while co-operating fully with the indemnifying party’s counsel, and without limiting the indemnifying party’s right to have sole control over the defense and settlement, and

- co-operate in all reasonable ways in the defence of the indemnified claim.

**9. Liability and Insurance**

9.1 The Sponsor will takeout or maintain the statutory patient insurance and/or any other statutory insurance to cover liability for injuries or death to the Subjects caused by the Institution’s inappropriate action or omission, including for the avoidance of doubt those of the Investigator and other Study personnel, if applicable due to local law. If a statutory patient insurance is provided by the Institution, or if Institution are covered by self-insurance or if Subject injuries or death are covered by national mandatory law, the Institution shall provide a certificate of its insurance or documentation of self-insurance to the Sponsor at request.

9.2 Sponsor as a public Danish body is self-insured according to Danish Law and Sponsors assets are sufficient to cover any contemplated self-insured liability assumed by Sponsor under this Agreement.

9.4 Without prejudice to the express indemnities for Subject claims under Section 8 and 9, neither Party shall be liable for any lost profits or sales or other indirect, incidental or consequential damage incurred by the other Party under or in relation to this Agreement.

9.5 A Party’s liabilities to the other Party under and in relation to this Agreement shall be limited to the aggregate total amount of the Study budget in Appendix B, except for any damage caused deliberately or by gross negligence.

**10. Term and Termination**

10.1 This Agreement shall be considered fully executed on the latest date that a Party executes the same, and will remain in effect until completion of the Study, close-out of Institution or completion of the obligations of the Parties under this Agreement or earlier termination in accordance with this Section 10 whichever occurs first.

10.2 This Agreement may be terminated by either Party at any time in the exercise of its sole discretion upon thirty (30) calendar days prior written notice to the other Party without justifying the reasons for termination.

10.3 Notwithstanding the above, Sponsor or Institution/Investigator may immediately terminate the Study if any patient safety, laws or regulations are violated. Upon receipt of notice of termination, Institution/Investigator agrees to promptly terminate the conduct of the Study to the extent medically permissible for any individual who participates in the Study. The total sums payable by Sponsor pursuant to this Agreement shall be equitably prorated for actual work performed to the date of termination.

10.4 Institution/Investigator shall immediately deliver to Sponsor all Data generated as a direct result of the Study and shall, at Sponsor’s expense return to Sponsor or destroy upon instructions of the Sponsor, all unused Study Product, all documents, materials and equipment provided by Sponsor and all Sponsor Confidential Information, as defined in Section 3, at the earlier of the conclusion of the Study or termination of this Agreement. This provision does not apply to those documents that should be maintained and retained by Institution/Investigator at Institution, as defined in the Protocol and as requested by applicable laws and regulations.

10.5 The rights and obligations of the Parties which by intent or meaning have validity beyond termination as set forth above, including, but not limited to, rights with respect to patent rights, ownership of Inventions, confidentiality, liability limitations, indemnification and insurance, and publication shall survive five (5) years after the termination or expiration of this Agreement.

**11. Applicable Law and Regulations**

11.1 The Parties shall comply with all applicable national and international laws, regulations and guidelines, especially those governing the conduct of clinical trials, dealings in medicinal products, responsibilities of clinical investigators, informed consents, protection and privacy of personal data and storage of data and records, including, without limitation, the ICH Guidelines and the European Guidelines on Good Clinical Practice (hereinafter referred to as “ICH-GCP”), Good Laboratory Practice, the revised versions of the Declaration of Helsinki Directive 95/46/EC and Directive 2001/20/EC of the European Parliament and of the Council, and professional industry association regulations.

11.2 The Parties agree that the collection, processing and disclosure of personal data and medical information related to the Study subject, and personal data related to Investigator and any investigational staff (e.g., name, hospital or clinic address and phone number, curriculum vitae) are subject to compliance with applicable personal data protection and security laws and regulations. Institution/Investigator shall not disclose to the Sponsor the identity of the subjects or information from which the identity of the subject can be deduced without prior written consent of the subject.

11.3 Institution/Investigator agrees to inform the investigational staff that their personal data may be collected. In such case the Sponsor may transmit such personal data to other affiliates or group companies and their respective agents worldwide. Nonetheless, Sponsor will apply adequate privacy safeguards to protect such personal data. Personal data may also be disclosed as required by individual regulatory agencies or applicable law, such as to report serious adverse events.

11.4 The Institution confirms that neither it, and to the best of its knowledge nor any of its investigators, employees, agents or other personnel providing services for the Study pursuant to this Agreement, has ever been debarred, disqualified, or banned from conducting Investigations or is under investigation by the competent authority or any equivalent regulatory authority within the US for debarment, disqualification or any similar regulatory action.

**12. Law and Venue**

12.1 In the event of any dispute arising between the Parties in relation to the terms of this Agreement, the Parties shall use their best endeavours to resolve the matter on an amicable basis. This Agreement shall be governed by and shall be construed in accordance with the laws of [.…] without regard to any conflicts of law’s provisions. The Parties consent to the competent courts of [….] for the resolution of all disputes or controversies between the Parties hereto that the Parties are unable to settle amicably.

**13. Miscellaneous**

13.1 Neither Party shall assign its rights or duties under this Agreement to another without prior written consent of the other Party. Subject to the foregoing, this Agreement shall bind and inure to the benefit of the respective Parties and their successors and assigns.

13.2 Institution is an independent contractor to Sponsor, and not a partner, agent, employee, representative, or joint-venture of Sponsor. Except as set forth in this Agreement, no Party, or its employees, agents, or subcontractors, has any right or authority to bind or act on behalf of another Party.

13.3 Investigator confirms that there is no conflict of interest that will inhibit or affect the Investigator’s performance under this Agreement and confirm that their performance under this Agreement does not violate any other agreement with third parties. For the avoidance of doubt, Institution and Investigator are free to enter into any other agreement with any third parties as long as this does not prevent Institution and/or Investigator from fulfilling their obligations according to this Agreement.

13.4 This Agreement may not be altered, amended or modified except by written document signed by the Parties.

13.5 If any of the provisions of this Agreement conflicts with any provision of the Protocol or any other relevant document, this Agreement shall take precedence.

13.6 This Agreement constitutes the entire agreement of the Parties with respect to the subject matter hereof. It expressly supersedes any prior or contemporaneous oral or written representations or agreements. The Appendices form an integral part of the Agreement. If any part of this Agreement is found to be unenforceable, the rest of this Agreement will remain in effect.

13.7 Any event beyond the reasonable control of a Party occurring after signing this Agreement, which a Party could not reasonably have taken into account at the time of the signing, which prevents or delays the affected Party from performing this Agreement or makes the performance unreasonably burdensome, and which the Party cannot overcome with reasonable loss of time or cost, shall constitute an event of force majeure. An event of force majeure releases the affected Party from performing this Agreement for the time the event lasts. The affected Party shall without delay inform the other Party of the event and its effects in writing. If the event continues for over sixty (60) days, either Party may terminate this Agreement in writing with immediate effect.

IN WITNESS WHEREOF, Sponsor and Institution executed this Agreement by signing below as of the date first written above.

For Institution: For and on behalf of Sponsor:

Date: Date:

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 Tine Sigsgaard

 Senior Consultant, Hospital Management

 Date:

 \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

 Billy Kristensen

 Head of Dept. Anaesthesiology and Intensive Care

 Date:

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 [Lone Musaeus Poulsen]

 [Primary Investigator, Dept. of Anaesthesiology and Intensive Care]

Investigator:

I hereby acknowledge that I have read and agree with the terms of this Agreement, and that I will act and perform my duties in the study in accordance with the content of this Agreement and the details outlined in the Appendices.

Date:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Investigator

 **If electronic signatures are applied to this contract only signatures from those stated above will actually be signing the contract. Additional electronic signatures from persons not mentioned above may be from persons considered important for the signature process, i.e. legal advisors, secretariats.**

**Appendix A – Protocol**

**Version 1.2 2017**

http://www.cric.nu/aid-icu-protocol/**(to be downloaded and saved as a file).**

**Appendix B – Budget**

Payment terms

|  |  |  |  |
| --- | --- | --- | --- |
| **Service** | **Time required** | **Hourly rate:**  | **Amount** |
| Inclusion of a patient |  |  | **100 EUR** |
| 90 days, and 1 year follow-up |  |  | **2 x 50 EUR** |
| **TOTAL PER PATIENT** |  |  | **max 200 EUR**  |

Monitoring will be performed for approx. 10% of patients, selected by a risk-based approach.

**General payment terms:**

Sponsor´s reports based on the electronic CRF records of patient status will be provided in quarterly intervals preferential in January, April, July, and October. Upon receipt of a formally correct invoice from Institution/Investigator the Payments under this agreement will be due, and will be payable to Institution, within 30 days (netto), after a valid and undisputed invoice is issued to the Sponsor. Payments are subject to the delay interest provisions in the applicable law.

Payments will be made per completed and valid patient, i.e. patients for whom all required data have been documented in the electronic Case Report Form (eCRF), all queries have been solved and the patient has been finalized in the eCRF. All procedures and complementary examinations will be performed as per routine practice. There are no study specific investigations. The payment details for transfer of payments, as advised by the Institution:

**Payee details (optional)**

The Parties agree that the payee designated below is the proper payee for this Agreement, and that payments under this Agreement will be made only to the following payee (“Payee):

|  |  |
| --- | --- |
| **Payee Name** | [INSERT] |
| **Payee Address** | [INSERT] |
| **Payee Email Address** | [INSERT] |
| **Bank Name** | [INSERT] |
| **Bank Address** | [INSERT] |
| **Bank Account Number** | [INSERT] |
| **Swift/BIC** | [INSERT] |
| **Tax ID Number** | [INSERT] |
| **Reference number** | [INSERT] |