Clinical Trial Agreement

with regard to the performance of the clinical trial:
"A double blind randomised, multicentre, active controlled, parallel-group, phase III trial to evaluate the efficacy, safety and pharmacokinetics of intravenous clonidine (hydrochloride) compared to midazolam for sedation in children from birth to less than 18 years of age."
(CloSed1)

hereinafter referred to as "**clinical trial**" or "**CloSed1**"

made by and between:

Universitätsklinikum Erlangen

Maximiliansplatz 2
91054, Erlangen, Germany
represented by the Commercial Director Dr. Albrecht Bender, acting on behalf of the

Department of Paediatric and Adolescent Medicine
Head: Prof. Dr. med. Wolfgang Rascher

CloSed Consortium
Scientific Coordinator: PD Dr. rer. nat. Antje Neubert

hereinafter referred to as **"UKER"**

and

Univerzita Karlova

Ovocný trh 560/5
Prague 1, 116 36, Czech Republic
represented by Prof. Aleksi Šedo, Dean of the First Faculty of Medicine

hereinafter referred to as "**UK**"

and

Všeobecná fakultní nemocnice v Praze

U Nemocnice 499/2
128 08 Prague 2, Czech Republic
represented by Mgr. Dana Jurásková, Ph.D., MBA, Hospital Director

hereinafter referred to as "**VFN**"

UK and VFN together hereinafter referred to as **"Study Site"**

Recitals

The clinical trial subject to this Agreement is implemented through the Project "Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit" (CloSed), approved and financed by the European Commission in the framework of the 7th Framework Programme for Research and Technological Development with Grant Agreement No. 602453, signed by all Project Beneficiaries. Both UKER and the UK are Beneficiaries of the CloSed Project; UKER is the Coordinator of the CloSed Project. Both UKER and UK have signed the CloSed Consortium Agreement, V.1 of 13 June 2013 and the 1st Amendment to the CloSed Consortium Agreement.

Details regarding the clinical trial are laid out in the Clinical Trial Protocol.

VFN has a long-term relationship with UK and for the purpose of this Clinical Trial Agreement (hereinafter referred to as "**Agreement**"), UK is to manage the administrative and financial aspects of the CloSed Project, while the study will be performed at VFN. UK warrants that all clinical trial activities are performed within the facilities of VFN and are carried out according to all applicable Czech and international rules. VFN agrees to performing the clinical trial in accordance with this Agreement. In order to be able to jointly fulfil the obligations of a CloSed study site, UK and VFN have the right to conclude a contract wherein they shall regulate their mutual relationships and division of responsibilities arising for the Study Site according to this Agreement.

MUDr. Pavla Pokorná, Ph.D., employee of Všeobecná fakultní nemocnice v Praze and employee of Univerzita Karlova, is the Principal Investigator of the Study Site. Hereinafter, she is referred to as "**Investigator**". The Investigator is willing to participate in the clinical trial sponsored by UKER.

Nothing contained in the contents of this Agreement constitutes a contractual relationship between the Investigator and UKER. Where this Agreement states any responsibilities, steps or obligations of the Investigator, these represent the obligations of the Study Site, which shall ensure that the Investigator fulfils them. Therefore, the Study Site declares that the Investigator will comply with all conditions of the Protocol and this Agreement.

The contracting parties conclude this Agreement, which defines terms and conditions of the cooperation in carrying out the clinical trial at the Study Site. CloSed1 shall be performed under the supervision of the Investigator in the Clinics of the Paediatric and Adolescent Medicine of VFN.

In accordance with Czech legislation, UK can be national trial coordinator in the Czech Republic for this clinical trial.

As a national coordinator of the clinical trial in the Czech Republic, UK may negotiate with Local and National Authorities as a delegated Sponsor representative in the Czech Republic for all matters related to the successful implementation of CloSed1 by the Study Site. For this purpose, UKER shall make available a Letter of Authorisation.

UKER as a Sponsor of the clinical trial has the right to assign Sponsor's tasks or responsibilities to any third party (appointee). Delegated tasks are listed in the document Sponsor's Delegation List, signed by both UKER and UK.

§ 1
Scope of the Agreement

(1) The scope of this Agreement shall be the participation of the Study Site in the multicentre clinical trial:

> "A double blind randomised, multicentre, active controlled, parallel-group, phase III trial to evaluate the efficacy, safety and pharmacokinetics of intravenous clonidine (hydrochloride) compared to midazolam for sedation in children from birth to less than 18 years of age." (CloSed1)

(2) The extent and the contents of the activities are specified in the clinical trial protocol on which this Agreement is based and which shall form an essential part hereof by reference.

§ 2
Legal Framework

The services provided hereunder shall be performed in accordance with the clinical trial protocol in its present or any amended future versions, the Grant Agreement No. 602453, the Consortium Agreement in the present or any amended future versions, all relevant national, i.e. Czech laws and regulations, the recommendations set forth in the ICH GCP (Harmonized Tripartite Guidelines for Good Clinical Practice) and the Helsinki Declaration, in each case as amended from time to time. The contracting parties agree to respect the before mentioned provisions.

§ 3
UKER's Obligations

(1) UKER or a third party delegated by UKER shall provide UK with all necessary documents for obtaining a favourable assessment from the relevant ethics committee and other relevant institutions (competent authorities, e.g. SUKL).

(2) UKER shall promptly inform the Investigator and the Study Site of all reported serious adverse events (SAE) in accordance with the applicable statutory provisions.

(3) In case of any amendments of the clinical trial protocol or in the event of early termination, UKER shall inform the Investigator promptly and discuss the further course of action. The Investigator and VFN agree to carry out the clinical trial at all time in accordance with the latest version of the clinical trial protocol. UKER or a third party delegated by UKER shall provide the Study Site any reviewed version of the clinical trial protocol immediately after such version comes into effect. The Investigator shall confirm the receipt thereof and, if necessary, forward the same to the Ethics Committee of VFN.

(4) The Investigational Medicinal Product (IMP) required for the performance of the examination shall be supplied by the manufacturer (UKER Hospital Pharmacy). directly to the VFN pharmacy. Handling of the IMP is described in the IMP Handling Instructions. Ordering, receipt and storage of the IMP is further described on the trial SOP "CL006 Standard Operating Procedure for Ordering and Distribution of IMPs".

(5) UKER shall ensure patient insurance as required by the clinical trial and all applicable laws, the insurance limit of which shall be in an amount adequate to the risks involved in the clinical trial. UKER has provided an insurance certificate to the Study centre in advance. The insurance certificate is attached hereto.

§ 4
Obligations of the Study Site

(1) The Study Site agrees to procure and maintain for the entire term of the clinical trial the conditions, including technical and human resources as necessary and required by the Investigator, for the performance of the trial in accordance with generally accepted scientific standards and all applicable rules, always exercising the highest level of diligence possible.

(2) The Study Site shall ensure that the Investigator is able to perform his or her duties as described in this Agreement at all times during the entire term of the clinical trial. In the event that the Investigator is no longer available at any time during the clinical trial, the Study Site shall promptly propose to UKER a physician sufficiently qualified to perform the trial as a replacement of the Investigator at the Study Site. Should the parties hereto fail to reach an agreement on the future replacement of the Investigator, then UKER shall be entitled to terminate this Agreement.

(3) The Study Site and the Investigator shall check the specific terms and conditions of the insurance made available by UKER for the purpose of conducting the clinical trial. The Study Site and the Investigator shall furthermore hand the insurance's terms and conditions over to the participants in the clinical trial, were required.

(4) The Study Site and the Investigator shall enable and support the performance of monitoring visits and, where applicable, the work of any third party documentation officers or information specialists as well as any potential audits carried out by persons or institutions designated by UKER and/or the competent supervisory authorities. For the SUKL, the Czech Competent Authority, the latest version of the instruction SUKL KHL 22, published at http://www.sukl.cz/leciva/podklady-k-oblasti-klinickych-hodnoceni, applies. For the performance of such audits and inspections, the Study Site and the Investigator shall make best efforts to grant said persons access to all original information obtained and documents generated in the course of the clinical trial, including, but not limited to, the patients' records.

(5) The Study Site shall enable and support the participation of the Investigator or a representative of the Investigator in any clinical trial meeting.

(6) The Study Site agrees to properly document all information required in accordance with all applicable laws and regulations and to retain all documents relevant to the clinical study in accordance with applicable provisions, but in any case for at least 15 years. The Study Site shall upon request make available such documents to UKER or a third party delegated by UKER or to any authority authorised for inspection by UKER within a reasonable period of time.

(7) The Study Site shall be responsible for obtaining a favourable opinion from the relevant ethics committee, as well as all other authorisations necessary for conducting the clinical trial at the Study Site's premises. Any related costs shall be borne by UK.

(8) Should the Study Site be unable to obtain a favourable opinion from the ethics committee or any other relevant authorisation, either party hereto shall be entitled to withdraw from this Agreement. In such case, no party shall have any claims for damages or lost profit against the other parties.

(9) The Study Site shall furnish a copy of the opinion of the ethics committee and SUKL's authorisation to UKER or a third party delegated by UKER promptly after receipt.

(10) The Investigator shall carefully read the clinical trial protocol and any amended version of the same and shall promptly notify UKER in case any modifications to the clinical trial protocol appear necessary in the opinion of the Investigator.

(11) If so requested by the ethics committee, the Investigator shall take care of any correspondence with the ethics committee having jurisdiction over the Investigator during the course of the clinical trial. To the extent possible, UKER or its appointee will support the Investigator in such correspondence.

(12) The Investigator shall ensure that the clinical trial is being carried out properly in accordance with the clinical trial protocol and in compliance with the applicable legal requirements, the standard operating procedures made available, and any other instructions issued by UKER or a third party delegated by UKER, as well as in accordance with generally accepted scientific standards. The Investigator shall exercise the highest level of diligence possible.

The Investigator warrants that he/she will not commence and proceed with the clinical trial unless the required Ethics Committee and Competent Authority approvals have been obtained and all other necessary documentation as requested by the protocol is in place, including consent for recruitment from UKER.

(13) The Investigator shall in particular ensure that only participants eligible for enrolment pursuant to the clinical trial protocol will be accepted in the trial. The Investigator has verified that he/she has a sufficient number of potential participants in the clinical trial.

(14) The Investigator shall ensure for each participant in the clinical trial prior to the commencement of any trial-specific activities, that the character, importance, and consequences of the trial have been fully disclosed to the participant and that the participant is being informed about the purpose and extent of the recording and use of personal data, including especially but not being limited to health data and that the legally required written informed consent is obtained from of the parents/legal representative of the patient, or from the patient, if of age. Consent must be given to the patient's participation in the clinical trial, to the fact that data recorded in accordance with the clinical study protocol is disclosed, transmitted and processed in compliance with the applicable law, i.e. the provisions of the Czech Act No. 101/2000 Coll. on Personal Data Protection, as well as to the fact that data is anonymised, or coded in the manner corresponding to the study documents. For this purpose, the Study Site shall be responsible to prepare proper consent forms in the Czech language using a template made available by UKER or its appointee in the most recently revised version. These informed consent forms must be approved by the relevant ethics committee. The Investigator is required to supply a re-translated English version of the informed consent forms and of any amended versions thereof to UKER.

(15) The Investigator is obliged to always act in the best interests of the participants in the study and in particular to deviate from the specifications of the clinical study protocol if it is necessary from a medical perspective. Any such emergencies shall be reported to UKER and all relevant third parties delegated by UKER immediately.

(16) The Investigator undertakes to notify UKER in pseudonymous form promptly (within 24 hours from obtaining the information) of any occurrence of a serious adverse event (SAE) in the course of the participation in the clinical trial.

(17) In the event of the death of a person involved in the clinical trial, the Investigator undertakes to provide UKER, the involved ethics committee, and any other competent authority with the additional information required under sec. 12(6) of the GCP Regulation.

(18) The Investigator shall instruct the Study Site's employees engaged in the clinical trial (physicians, co-investigators, study nurses, documentation officers/information specialists, temporary staff) on the clinical trial process in accordance with the clinical study protocol and shall make sure in regular intervals that said employees are carrying out their trial-related tasks in a diligent and correct manner. UKER shall have the right to store the names and office addresses of the Investigator and the said employees in a dedicated non-public study database if all legal regulations are fulfilled.

(19) The Investigator shall ensure that all patient data relevant for participation in the clinical trial is documented sufficiently and completely. The Investigator shall promptly complete or cause the completion of the web-based electronic Case Report Forms (CRF) in full and in accordance with the specifications contained in the clinical trial protocol. The Investigator shall correct any errors occurred, if any, immediately after such errors have been detected. In case the quality of the documentation is insufficient, UKER shall be entitled to exclude the Study Site from further participation in the clinical trial.

(20) The Investigator shall promptly notify UKER in writing of any deviations from the clinical trial protocol.

(21) Upon request, the Investigator shall, within an adequate period (e.g. 4 weeks), make appointments with monitoring officers designated by UKER and, upon such monitoring officers' visit, discuss the course of the clinical trial in an appropriate manner, follow their instructions, and be available for their queries.

(22) Upon being notified that the maximum number of patients specified in the most recent version of the clinical trial protocol with respect to a specific region, country, or an individual study centre has already been included in the clinical study, the Investigator shall not recruit any further patients for the trial.

(23) All information obtained by the Study Site in the course of the clinical trial must be made available to UKER or a third party delegated by UKER.

(24) Unused vials of IMP in this trial are to be destroyed on-site and the relative cost is covered by UK's budget and EU funds within the CloSed Project.

§ 5
Recruitment Target

The recruitment target given in the Description of Work of the Grant Agreement No 602453 shall apply with the additions specified in this § 5. UKER intends to include an aggregate number of at least 270 participants in the clinical study during the term of the study. Recruitment of such participants shall be performed in a competitive manner and shall cease upon achievement of the designated number of participants. Individual study sites must cease recruiting once the maximum number of 150 patients specified for a single Study Site has been procured, even if the total maximum number of patients for the overall clinical study has not yet been achieved. The Study Site will be notified of the cessation of recruitment by UKER. After receipt of such notice, the Study Site is not permitted to take on any further participants and any such inclusion of participants in excess will not be remunerated.

§ 6
Confidentiality

Regarding confidentiality, Section 10 of the Consortium Agreement, in its present and any amended future versions, shall apply

§ 7
Publications

Regarding publications, Article II. 30 of the Grant Agreement 602453 and Section 8.6 of the Consortium Agreement, in its present and any amended future versions, shall apply.

§ 8
Information, Data, Results, Patents

Regarding information, data, results and patents, Section 8 of the Consortium Agreement, in its present and any amended future versions, shall apply

§ 9
Remuneration

(1) Regarding remuneration, Section 7 of the Consortium Agreement, in its present and any amended future versions, shall apply. The project funds are transferred by UKER as Coordinator of the financed FP7 project solely to the Project Beneficiary UK.

(2) As defined in Annex I (Description of Work) to Grant Agreement 602453, the maximum per patient fee for each accurately included and fully documented participant in the clinical trial for whom UKER has received complete data records is € 2.500,00. Such fees are part of a larger budget assigned to UK as Beneficiary in the CloSed Project.

(3) The cost for destruction of unused vials on-site is also covered by the budget assigned to UK as Beneficiary in the CloSed Project.

(4) UK shall pay VFN up to 5.000 € for the fulfilment of its obligations contained in this Agreement. This sum will be reported by UK, as Beneficiary of the CloSed Project, as a subcontract in its financial reports to the European Commission. VFN and UK shall conclude a separate contract where their mutual financial relationships shall be regulated.

(5) The costs of participation to the clinical trial, as described in the CloSed Grant Agreement, are subject to the rules and regulations of the European Commission and the 7th Framework Programme for Research and Technological Development on the reporting and financial eligibility of expenditures. No lump sums shall be reported.

§ 10
Effective Date, Terms and Termination

(1) The contracting parties are informed that contracts concluded by UK and/or VFN have to be disclosed in the Register of Contracts, according to Art. 2 sect. 1 of the Czech Act nm. 340/2015 Coll. on the Register of Contracts. This action shall be referred to as "Disclosure" hereinafter.

(2) This Agreement shall become effective on its date of Disclosure. The Disclosure of this contract is the obligation of UK. UK shall inform UKER and VFN of the Disclosure of this Agreement and its effective date without undue delay. The information should be sent by email to the following addresses:
for UKER: closed@uk-erlangen.de, antje.neubert@uk-erlangen.de
for: VFN smlouvy@vfn.cz

(3) This Agreement may be terminated by UKER, UK and VFN if one of the other parties has committed a breach of one or more material obligations arising out of or in connection with this Agreement, including in particular, but not limited to, fraud or any illegal act in connection with or concerning this Agreement.

(4) UKER shall be entitled to terminate the clinical trial at any time and thus terminate this Agreement without notification of the reason.

(5) Notice of termination shall be given in writing (transmission by fax being sufficient). Upon receipt of a notice of termination, the Investigator shall no longer be permitted to take on further patients into the clinical trial.

(6) Besides the aspects covered by the clinical trial insurance provided by UKER, the Study Site shall not be entitled to claim any additional remuneration in addition to the remuneration set by § 9 of this Agreement.

§ 11
Final Provisions

(1) This agreement shall be governed exclusively by German law, excluding its conflict of law provisions. The parties further agree that any dispute arising out of this Agreement or in connection therewith, shall be resolved by the competent court in Erlangen.

(2) The conduct of the clinical trial in the Czech Republic by the Study Site shall be performed in accordance with §2 of this document, i.e. according to the clinical trial protocol in its present or any amended future versions, the Grant Agreement No. 602453, the Consortium Agreement in the present or any amended future versions, all relevant national, i.e. Czech laws and regulations, the recommendations set forth in the ICH GCP (Harmonized Tripartite Guidelines for Good Clinical Practice) and the Helsinki Declaration, in each case as amended from time to time.

(3) If any of the provisions of this Agreement is invalid or unenforceable, such invalidity or unenforceability shall not affect the validity and enforceability of the remaining provisions hereof. The parties hereto shall agree on a valid and enforceable replacement provision which comes as close as possible to the invalid or unenforceable provision.

(4) This Agreement constitutes the entire agreement between the parties with respect to the subject matter hereof. Any changes, amendments, modifications of or additions to this Agreement must be in writing. The parties hereto waive their right to annul this Agreement of written form by implication. Any annulment of the requirement of written form established by the intent of the parties may only be effected in writing.

(5) For the purpose of communicating any information to the Study Site, the parties agree, unless explicitly stated otherwise or unless the character of the matter implies directly otherwise, that UKER shall inform both UK and VFN.

(6) VFN confirms to have been supplied the following documents by UK in their latest approved versions, on the date of signature of this Agreement: CloSed Grant Agreement, CloSed Consortium Agreement, CloSed1 Clinical Study Protocol.

Annexes:

1. Insurance certificate for the CloSed1 clinical trial
2. IMP Handling Instructions
3. Sponsor's Delegation List

In Prague, dated:

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For the Study Site

prof. Aleksi Šedo
Aleksi Šedo, Dean of the Faculty of Medicine

Mgr. Dana Jurásková, Ph.D., MBA
Director of the General Faculty Hospital in Prague

In Erlangen dated:

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UKER

Dr. Albrecht Bender
Sales Manager

Prof. Dr. med. Wolfgang Rascher
The Chief of the Division of Paediatric and Adolescent Medicine

PD Dr. rer. nat. Antje Neubert
Scientific Coordinator
CloSed Consortium

The Investigator signs this Agreement in witness of her approval of its contents and to confirm that she complies with the qualification criteria necessary for the participation in the clinical trial. With her signature, she further confirms that she is not aware of any facts or reasons for which she should not be able to act as an investigator in this clinical trial and that the Ethics Committee having jurisdiction over her up to now has not objected to her activity as an investigator in clinical trials.

In Prague, dated

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Dr. Pavla Pokorná, PhD
The Lead Investigator