Cerebral **V**asospasm **A**fter **S**ubarachnoid Hemorrhage - **T**reatment

- VAST Study

- a multicenter, international, prospective observational clinical trial

Version: 1.0

Anticipated start of the study: July 01, 2023

GENERAL INFORMATION

Sponsor of the Study	Medical University Innsbruck
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Sub-investigator	**Dr. Philipp Geiger** Department of Neurosurgery Medical University Innsbruck Anichstrasse 35, 6020 Innsbruck philipp.geiger@tirol-kliniken.at
Sub-investigator	**Univ.-Prof. Dr. Claudius Thomé** Department of Neurosurgery Medical University Innsbruck Anichstrasse 35, 6020 Innsbruck claudius.thome@tirol-kliniken.at

SIGNATURES

Study Title:	Cerebral **V**asospasm **A**fter **S**ubarachnoid Hemorrhage - **T**reatment A multicenter, international, prospective observational clinical trial
Short Title:	VAST-Study

Declaration of the sponsor

The present clinical investigation plan (CIP) was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the product as well as with moral, ethical and scientific principles of good clinical practice (GCP), the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements.

With the signature below the person confirms to have read this Clinical Investigation Plan and to agree that it contains all information required for study performance. Furthermore, the person agrees to conduct the study as set in this CIP and to adhere to the sponsor's standard operation procedure (SOPs), if provided and as far as agreed. It has been understood that all documentation previously not published will be kept confidential. Furthermore, the person agrees to take all necessary measures to ensure safety and confidentiality of the patient´s identities.

Name of Sponsor Representative Medical University Innsbruck Head of OU	_____ Place, Date Signature

Declaration of the authors, the principal investigator and the statistician

The present CIP was subject to critical review. Its content is consistent with the current risk/benefit evaluation as well as with moral, ethical and scientific principles of GCP, the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements.

With their signature below the persons confirm to have read this Clinical Investigation Plan and to agree that it contains all information required for study performance. Furthermore, the persons agree to conduct the study as set in this CIP and to adhere to the sponsor's SOPs (as far as agreed and provided). It has been understood that all documentation previously not published will be kept confidential. Furthermore, the persons agree to keep patient´s identities in strictest confidence and to take all required measures to ensure this confidentiality.

PD Dr. Ondra Petr, MD, PhD, DBA Medical University Innsbruck Neurosurgical Senior Consultant and Principal Investigator	_____ Place, Date, Signature
Prof. Dr. Claudius Thomé Medical University of Innsbruck Chairman of Department of Neurosurgery	_____ Place, Date, Signature

LIST OF THE STUDY SITES

List name and address of each study site and study site investigator/s including full contact details such as telephone/fax number and email address as shown below:

A01	**Department of Neurosurgery**, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria **Principal Investigator** Priv.-Doz. Dr. Ondra Petr, MD, PhD, DBA Senior consultant / Faculty / Staff Head of Neurovascular Division Head of Neurotraumatology Division Head of Neurosurgical Intensive Care Unit @: ondra.petr@i-med.ac.at @: ondra.petr@yahoo.com **Sub-Investigator/s** Prof. Dr. Claudius Thomé, Chairman Department of Neurosurgery @: claudius.thome@tirol-kliniken.at Dr. Christian Preuss-Hernandez Neurosurgical Consultant @: christian.preuss-hernandez@tirol-kliniken.at Dr. Philipp Geiger Neurosurgical Resident @: philipp.geiger@tirol-kliniken.at
A02	Department of Neurosurgery, Landeskrankenhaus Feldkirch, Feldkirch, Austria.
A03	Department of Neurosurgery & Neurorestauration, Klinikum Klagenfurt, Klagenfurt, Austria.
A04	Department of Neurosurgery, Medical University Graz, Graz, Austria.
A05	Department of Neurosurgery, Kepler University Hospital GmbH, Johannes Kepler University, Linz, Austria.
A06	Department of Neurosurgery, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria.
A07	Department of Neurosurgery, Medical University of Vienna, Vienna, Austria.

A08	Department of Neurosurgery, Klinik Donaustadt, Vienna, Austria.
A09	Department of Neurosurgery, General Hospital Wiener Neustadt, Wiener Neustadt, Austria.
A10	Unit of Neurosurgery, Klinik Landstrasse, Vienna, Austria.
A11	Department of Neurosurgery, University Hospital of St. Poelten, Karl Landsteiner University of Health Sciences, St. Poelten, Austria.
A12	Department of Neurosurgery, University Hospital Ostrava, Ostrava, Czech Republic.
A13	Department of Neurosurgery, Ceske Budejovice Hospital, Ceske Budejovice, Czech Republic.
A14	Department of Neurosurgery, Pilsen University Hospital, Pilsen, Czech Republic.
A15	Department of Neurosurgery, Motol University Hospital, Prague, Czech Republic.
A16	Department of Neurosurgery, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic.
A17	Unit of Neurosurgery, Municipal Hospital - Ostrava Fifejdy, Ostrava, Czech Republic.
A18	Department of Neurosurgery, University Hospital Kralovske Vinohrady, Prague, Czech Republic.
A19	Department of Neurosurgery, University Hospital Olomouc, Olomouc, Czech Republic.
A20	Department of Neurosurgery, Usti Nad Labem Hospital, Usti Nad Labem, Czech Republic.
A21	Department of Neurosurgery, Liberec Hospital, Liberec, Czech Republic.
A22	Unit of Neurosurgery, Homolka Hospital, Prague, Czech Republic.
A23	Department of Neurosurgery, University Hospital Brno and Masaryk University, Brno, Czech Republic.
A24	Unit of Neurosurgery, Zlin Hospital, Zlin, Czech Republic.
A25	Unit of Neurosurgery, Pardubice Hospital, Pardubice, Czech Republic.
A26	Department of Neurosurgery, St. Anne's University Hospital Brno and Masaryk University, Brno, Czech Republic.
A27	Department of Neurosurgery and Neuro-Oncology, 1st Medical Faculty, Central Military Hospital, Charles University, Prague, Czech Republic.

SITE SPECIFIC SIGNATURES

Study Title:	Cerebral **V**asospasm **A**fter **S**ubarachnoid Hemorrhage - **T**reatment A multicenter, international, prospective observational clinical trial
Short Title:	VAST-Study

Declaration of the principal (site specific) investigator and his substitute

The present CIP was subject to critical review. Its content is consistent with the current risk/benefit evaluation well as with moral, ethical and scientific principles of GCP, the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements.

With their signature below the persons confirm to have read this CIP and to agree that it contains all information required for study performance. Furthermore, the person agrees to conduct the study as set in this CIP and to adhere to the sponsor's SOPs (as far as agreed and provided). It has been understood that all documentation previously not published will be kept confidential. Furthermore, the persons agree to keep patient´s identities in strictest confidence and to take all required measures to ensure this confidentiality.

It is agreed that the clinical trial will be conducted according to Austrian pharmaceutical act (AMG) as well as to the ICH-GCP Guideline (ICH-E6, CPMP/ICH/135/95) and the latest version of the Declaration of Helsinki.

To ensure data quality, clinical trial´s integrity and compliance with the CIP as well as with the various legal and regulatory requirements the sponsor will visit the participating sites.

With their signature below the persons agree to support visits of authorized persons (e.g. representatives of the sponsor) and to provide them directly to enter the source and other relevant documents in regard to the clinical trial (e.g. CRF, patient files).

Prof. Dr. Claudius Thomé Chairman Department of Neursurgery Medical University Innsbruck	_____ Place, Date, Signature

Additional involved persons and institutions

List name and address of each additional involved person or institution including full contact detail such as telephone/fax number and email address as shown below:

Data management	Department of Neurosurgery of Medical University Innsbruck, Austria Priv.-Doz. Dr. Ondra Petr, MD, PhD, DBA Senior consultant / Faculty / Staff Head of Neurovascular Division Head of Neurotraumatology Division Head of Neurosurgical Intensive Care Unit @: ondra.petr@i-med.ac.at @: ondra.petr@yahoo.com Dr. Christian Preuss-Hernandez Neurosurgical Consultant @: christian.preuss-hernandez@tirol-kliniken.at Dr. Philipp Geiger Neurosurgical Resident @: philipp.geiger@tirol-kliniken.at
Monitoring	Department of Neurosurgery of Medical University Innsbruck, Austria Priv.-Doz. Dr. Ondra Petr, MD, PhD, DBA Senior consultant / Faculty / Staff Head of Neurovascular Division Head of Neurotraumatology Division Head of Neurosurgical Intensive Care Unit @: ondra.petr@i-med.ac.at @: ondra.petr@yahoo.com Dr. Christian Preuss-Hernandez Neurosurgical Consultant @: christian.preuss-hernandez@tirol-kliniken.at Dr. Philipp Geiger Neurosurgical Resident @: philipp.geiger@tirol-kliniken.at
Statistics	Department for Biomedical Statistics of Medical University Innsbruck

TABLE OF CONTENT

GENERAL INFORMATION **1**
SIGNATURES **2**
Declaration of the sponsor **2**
LIST OF THE STUDY SITES **4**
SITE SPECIFIC SIGNATURES **6**
ABBREVIATIONS AND DEFINITIONS **10**
Information concerning the clinical trial: 11
Time period recruitment: 2 years with 12 months follow-up 11
Planned start (FPFV): July 01, 2023 11
Planned end of trial (LPLV): July 01, 2026 11
1. INTRODUCTION **12**
1.1 Study background 12
1.2 Current treatment management of CVS & DCI after aneurysmal SAH at Department of Neurosurgery of Medical University Innsbruck 12
1.3 Need of the study 13
1.4 Risk-benefit analysis 13
1.5 Transferability assessment of expected project outcome for practical use 14
2. STUDY OBJECTIVES **14**
2.1 Primary objective 14
2.2 Secondary objectives 14
3. STUDY DESIGN **14**
3.1 Study description 14
3.2 Endpoints 15
3.3 Timetable 15
4. STUDY POPULATION **16**
5. STUDY PROCEDURES **16**
5.1 General study procedures and assessments schedule 16
5.2 Study assessments 16
5.3 Closure of the study 16
6. MATERIAL AND METHODS **16**
7. DOCUMENTATION **17**
7.1 Data recording 17
7.2 Data storage 17
8. STATISTICS **17**

8.1 Randomization 17
8.2 Statistical design, methods and analysis process 17
9. QUALITY MANAGEMENT 18
9.1 Qualifications 18
9.2 Monitoring 18
9.3 Audits and inspections 19
10. REPORTING 19
10.1 Final study report 19
10.2 Publication 19
11. AMENDMENTS 20
12. ETHICAL AND REGULATORY ASPECTS 20
12.1 Responsibilities of the sponsor and investigator(s) 20
12.2 Approval of ethics committee and notification to authority 20
12.3 Data protection and confidentiality 21
12.4 Financing 21
12.5 Regulatory aspects 21
13. REFERENCES 22
14. APPENDICES 23

ABBREVIATIONS AND DEFINITIONS

CIP	Clinical Investigation Plan
CPP	Cerebral Perfusion Pressure
GOS-E	Extended Glasgow Outcome Scale
mRS	Modified Rankin Scale
eCRF	electronic Case Report Form
EC	Ethics committee
DCI	Delayed Cerebral Ischemia
GCP	Good Clinical Practice
CSF	Cerebral Spinal Fluid
ISF	Investigator Site File
ICP	Intracerebral pressure
PCI	Principal Investigator
aSAH	Aneurysmal subarachnoid hemorrhage
PI	Principal Investigator
TMF	Trial Master File
CVS	Cerebral Vasospasm
CT	Computed Tomography
EVD	External Ventricular Drain
DSA	Digital subtraction angiography
TCD	Transcranial Doppler Sonography

Study title	Cerebral **V**asospasm **A**fter **S**ubarachnoid Hemorrhage – **T**reatment – **VAST Study** A multicenter, international, prospective observational clinical trial
Research subject	Patients treated after aneurysmal SAH
Indication	aSAH from a ruptured intracranial aneurysm
Design of clinical trial	Observational
Number of trial sites	Multicenter, international with a planned number of 29 centers
Duration of clinical trial / timetable	Information concerning the clinical trial: Time period recruitment: 2 years with 12 months follow-up Planned start (FPFV): July 01, 2023 Planned end of trial (LPLV): July 01, 2026
Objectives (Primary/Secondary)	**Primary objective:** A detailed mapping of contemporary yet most likely various treatment strategies for CVS and DCI after aSAH with their resultant outcomes **Secondary objective:** Identification of the optimal treatment strategy for CVS and DCI after aneurysmal SAH. Initiation of further randomized controlled trial Ultimately, international treatment guidelines for CVS & DCI after aSAH shall be proposed and provided in the future.
Endpoints (primary / secondary)	Final neurological outcome in SAH patients treated by different strategies for CVS & DCI across the European neurosurgical centers
Study design	A prospective, multicenter, non-randomized, observational trial analyzing contemporary treatment strategies for CVS and DCI after aSAH across the European referral neurovascular centers

1. INTRODUCTION

1.1 Study background

Cerebral vasospasm (CVS) alongside the delayed cerebral ischemia represent specific feared detrimental events related to aneurysmal subarachnoid hemorrhage (aSAH) that are associated with permanent neurological morbidity (deficits) in approximately 15% of the affected patient population.[1,2]
In defiance of unceasing both basic and clinical research, there is still no consensus how to prevent and/or specifically treat these. Besides known his prior treatment strategies such as blood pressure targeting or pharmacological treatment with vasodilators as nimodipine or similar, there are many other emerging approaches, for instance analysis of various parameters and biomarkers from blood and CFS samples, or using the multimodal neuromonitoring techniques[3-8]. The aforementioned various methods enable a wide range of treatment possibilities, on that account presently leading to utterly heterogenous therapy of CVS and DCI across the European and North American centers.
For instance, even within the ambit of one specific medication - a vasodilator drug nimodipine - there are several different ways how to administer this, ranging from single intraarterial application to continuous intraarterial pharmacological infusion[9].

At present, no accepted treatment guidelines exist. In addition, most research data dealing with CVS are rather scarce and oftentimes contradicting.

Paying heed to not negligible CVS incidence afflicting more than 40% of cases, resolution of CVS treatment along with new established guidelines with their implementation in contemporary SAH management represents a priority in a daily neurosurgical and neurointensive care practice, most likely resulting in better clinical outcome.

1.2 Current treatment management of CVS & DCI after aneurysmal SAH at Department of Neurosurgery of Medical University Innsbruck

According to our institution's standards of care, after an emergency interdisciplinary case discussion with other neurovascular experts on call, a very early occlusion of the ruptured aneurysm regardless of chosen treatment modality, either surgical or endovascular, pertains to the first steps of our current SAH management. This eliminates the causality of the aneurysmal SAH. Thereafter, neurointensive care management alongside the strict monitoring of various cerebral and other vital, laboratory and physical parameters are performed for the next at minimum two weeks after the initial hemorrhagic event. Of note, all patients receive prophylactically nimodipine medication. In high-grade SAH patients nimodipine is commonly administered intravenously in a continuous fashion (10mg of nimodipine diluted in 50ml NaCl 0.9% - isotonic saline with an infusion rate of 4 to 10ml/h adapted to MAP). Low-grade SAH patients are usually treated with oral nimodipine, with a dose ranging from 180 to 360 mg per day. Likewise, MAP is prophylactically maintained above 80 mmHg.

Transcranial Doppler examination (TCD) is routinely performed on a daily basis (twice a day) to monitor SAH-associated CVS and DCI. In case of newly diagnosed moderate or severe CVS or as a

routine measure in all patients, digital subtraction angiography (DSA) is performed mostly between day 7 to 12 after initial aneurysm treatment (= initial hemorrhagic event). If CVS is confirmed, nimodipine in an intraarterial fashion is administered after interdisciplinary oral agreement with the other neurovascular experts being on call, with a dose leaving to the discretion of the attending neuroradiologist. Of course, both exact dosage and vascular response to the CVS are recorded and documented in detail.

In addition, induced hypertension with a target MAP of > 90 mmHg is used to optimize cerebral perfusion.

Multimodal neuromonitoring – both ICP probe and $PtbO_2$-probe are inserted routinely in all non-responsive patients with a Glasgow comma scale of $\leq$ 8. In a selected patient population, additional cerebral (continuous) microdialysis and/or external ventricle drainage (EVD) are also applied. Given the current internationally worldwide accepted critical thresholds of ICP and PbtO2 in adults, we aim to keep the ICP under 22mmHg as well as PbtO2 values over 20mmHg. To achieve these, our contemporary staircase treatment algorithm for the intracranial hypertension is fundamentally based on the Seattle International severe traumatic brain injury consensus conference (SIBICC). At our institution, the original eight-tier treatment design for the starting from intubation with normocarbic ventilation (tier I), followed by increased sedation (tier II), ventricular CSF drainage and/or lumbar drainage (tier III), hyperosmolar therapy with mannitol and hypertonic saline (tier IV), induced hypocapnia (tier V), hypothermia (tier VI), metabolic suppression (barbiturates, tier VII) with the last most invasive measure decompressive craniectomy (tier VIII) has been always tailored to the medical conditions of the patient with an individualized targeted therapy.

1.3 Need of the study

Since neither international consensus nor guidelines for monitoring and management of cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH) exist, this international multicenter observational study aims to systematically track the contemporary treatment approaches across the European referral neurovascular centers with their individualized differences and the resultant outcomes in a prospective study design. Thereafter, by comparing the data, optimal treatment management for CVS and DCI after aneurysmal SAH may be identified. In this instance further randomized controlled trial will be conducted (as a new study). Ultimately, international guidelines shall be proposed and provided in the future.

1.4 Risk-benefit analysis

There will be no direct benefit or risk to the patient, no study-related measures or alterations of the current therapy are required.

1.5 Transferability assessment of expected project outcome for practical use

The contemporary treatment management and monitoring strategies for CVS and DCI after aneurysmal SAH the Central and Western Europe will be appraised. Multiple parameters (attached to this file) will be recorded and documented. Subsequently, a detailed analysis and evaluation will be performed. The results will be presented in the international conferences and congresses.

Consequently, by comparing the detailed data with various treatment algorithms across the European referral (tertiary) neurovascular centers an optimal clinical treatment management for CVS and DCI after aneurysmal SAH resulting in the best possible outcome might be identified. In this instance, as a next consequent step, a future randomized controlled trial will be initiated to confirm the findings. Ultimately, international guidelines shall be proposed and provided in the future.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to systematically collect clinical data on treatment management for CVS and DCI after SAH across the European referral neurovascular centers. This allows a detailed mapping of contemporary yet most likely various treatment strategies with their resultant outcomes.

2.2 Secondary objectives

The secondary objective is to identify the optimal treatment strategy for CVS and DCI after aneurysmal SAH. Moreover, depending on the findings, further randomized controlled trials might be initiated. Ultimately, international guidelines shall be proposed and provided in the future.

3. STUDY DESIGN

3.1 Study description

A prospective, international, multicenter, observational study

Number of neurovascular centers involved:

At present, all 11 Austrian neurosurgical centers and all 16 centers in the Czech Republic will participate in the study. Henceforth, other neurovascular centers will most likely be also involved in the study. All SAH patients with a diagnosed (confirmed) ruptured intracranial aneurysm from all participating centers will be consecutively included in the study. Various parameters will be recorded and documented throughout the hospital stay of the patient in the spreadsheet designated for this study (*see the attachments*).

3.2 Endpoints

3.2.1 Primary endpoint

Assessment of neurological outcome of SAH patients at discharge, 6 and 12 months after initial hemorrhagic event at the participating centers.

3.2.1.1 Excel / REDCap sheet description

An Excel sheet and REDCap file will be distributed to all participating centers. Patient demographics, SAH grading, aneurysm characteristics, type of intervention, ICU management, neuromonitoring, CVS diagnostics and treatment strategies and outcome parameters, among others will be recorded and documented in detail. The file(s) (spreadsheet) designated for this study is attached to the project proposal.

3.2.2 Secondary endpoints

Assessment of possible variance across the participating centers with the resulting outcomes.

3.3 Timetable

5 *Year*	*2023*				*2024*				*2025*				*2026*			
Quarterly period	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Organization																
Observation and documentation of implemented treatments for CVS & DCI																
Follow-up at 6/12 months																
Preliminary data analysis																
Final data analysis																
Manuscript writing																

4. STUDY POPULATION

This prospective observational study will be performed in a multicenter and international fashion. Given the study design and its observational nature, there will be an arbitrary number of the included patients during the given 2-year time frame of the study, most likely corresponding with the epidemiological prevalence of SAH in the Central and Western Europe.

5. STUDY PROCEDURES

5.1 General study procedures and assessments schedule

Data will be collected in an observational prospective study design focusing on the treatment management and strategies for CVS and DCI from the participating European centers. Data shall be documented on a daily basis in order to minimize errors and bias.
At the close of the study conclusions will be drawn based on the study findings.

5.2 Study assessments

5.2.1 Excel sheet / REDCap file

For the full excel sheet, please see the appendix.

5.3 Closure of the study

The study period is initially designed for 2 years (24 months) with ensuing 6 and 12 months of follow-up visits. The trial ends when all centers will submit their complete documentation of all consecutive SAH patients with their used treatment algorithm in the given time frame. The completion of the study will be reported to the ethics committee as well as to the relevant authorities.

6. MATERIAL AND METHODS

All Austrian and Czech as well as other participating European neurosurgical centers treating aneurysmal SAH on a regular basis will be screened for participation. Department chairmen will be contacted through email. Participating centers will be provided with the above-mentioned Excel sheet / REDCap file. Amendable / authorized staff will document their standard of care with a particular focus on CVS and DCI. An exact number of the presumptive SAH patients is rather difficult to predict, yet taking into account that aneurysmal SAH has a global incidence of approximately 8 persons per 100.000 person-years, we expect a SAH patient population of 700 per year. For instance, given the estimated CVS rate of 20-40%, this would account for approximately 200 SAH patients suffering from CVS / DCI in Austria.

7. DOCUMENTATION

The conduct of the study in agreement with the GCP-guidelines and the investigational plan as well as the accuracy of all data documented in the eCRF are the responsibility of the principal investigator. All collected data of this study will be recorded and documented in the provided eCRF / spreadsheet by appropriate authorized persons.

The data will be pseudo anonymized. The structured Excel sheet is attached in the appendix.

7.1 Data recording

From all participating centers sensitive data are not allowed to be used to backtrack patients outside of the clinical setting. The data will thereafter be sampled according to the used methods for CVS and DCI treatment.

7.2 Data storage

7.2.1 Storage duties of sponsor

The Sponsor has to keep all study-relevant documents of the completed or discontinued clinical trial after completion or discontinuation of the study for a minimum of 15 years.

7.2.2 Storage duties of investigator(s)

The sponsor will keep the gathered data and results readily available for at least 15 years.

8. STATISTICS

Statistical analysis will be performed by the Department for Biomedical Statistics of the Medical University Innsbruck, Austria.

8.1 Randomization

There will be no randomization.

8.2 Statistical design, methods and analysis process

8.2.1 Target variable

Primary endpoint: Appraisal of various contemporary treatment strategies for CVS and DCI after aneurysmal SAH across the participating centers based on the international multicenter observational design of the study

Secondary endpoint: Proposal of new randomized controlled trial based on the findings if identifying the optimal treatment strategy

8.2.2 Definition of analysis sets / populations / subgroups

Consecutive SAH patients harboring a diagnosed / confirmed ruptured intracranial aneurysm, subgroups will be post hoc defined according the used particular treatment strategies for the CVS and DCI.

8.2.3 Interim analysis

After a time period of 12 months, an interim analysis will be performed.

8.2.4 Handling of missing, unused or spurious data, including drop-outs and withdrawals

This data will be documented and will be described in the methods section in the publication. Informed and written consent will be obtained from the patient or her/his legal guardian. Due to its observational nature, there will be no risks or benefits for the patients. Any drop-outs will be noted and documented.

8.2.5 Data analysis

Department of Biomedical Statistics of Medical University Innsbruck, Austria.

9. QUALITY MANAGEMENT

Training, monitoring and regular meetings will be performed for quality assurance within this clinical study in order to comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data.

9.1 Qualifications

The sponsor is responsible for selecting the investigator(s) / institution(s). Each investigator will be qualified by training and experience and will have adequate resources. Each individual involved in conducting a trial will be qualified by education, training and experience to perform his or her respective task(s) (see ICH GCP E6).

9.2 Monitoring

A brief summary of the study be given, where fundamental activities and possible additional measures taken to ensure quality across trial sites as well as information pathways are described.

The trial sites will be supervised by the leading center (Medical University Innsbruck) to ensure the quality of the collected data.

All investigators agree that the supervisor regularly visits the trial site and assure that his delegate will receive appropriate support for the tasks at the trial site, as agreed in separate contracts

with each trial site. The investigator will secure access to all necessary documentation for trial-related check.

9.3 Audits and inspections

Regulatory authorities, ethics committees, and Sponsor's delegates may perform on-site inspections or audits, for which the Investigator must provide support at all times.
During an audit, following issues among other things will be inspected:

- performance of the clinical trial according to the investigation plan
- data validity
- quality of the clinical trial according to the ICH E6 guidelines

After each external audit an audit-certificate by the auditor has to be sent to the investigator. This certificate has to be kept in the ISF to evidence the audit to the regulatory authorities in the case of an inspection by them. The audit-report is sent to the sponsor of the study. An audit-certificate will be attached to the final report at the end of the study.

10. REPORTING

For the documentation of the progress and development of the study, protocols about the meetings of the various group committees might be necessary.

10.1 Final study report

All information regarding this clinical study has to be kept in confidence. The statistical analysis and the integrated final study report will be prepared according to ICH E6 and finalized within 12 months after the last received data. The final study report will be reviewed and signed by the sponsor, the investigator and all further responsible persons. All information in that report is strictly confidential.

Finally, the investigator will sign the final study report of the clinical trial. This confirms that the report describes implementation and results of the clinical trial by the best of his knowledge.

10.2 Publication

The following shall be designated:

- **Authorships**: Ondra Petr (PI), Christian Preuss-Hernandez, Philipp Geiger, Claudius Thomé, & other sub-investigators from the other centers contributing to this study
- intermediate or partial results will be published
- the aim is to publish in a PubMed listed journal

The presentation of the results in a publication should have the extent of the defined framework of the CONSORT-Statement (www.consort-statement.org). All randomized and controlled clinical

studies, which recruits patients after the 1st of July 2005, have to be registered in a publicly available data base (e.g. www.clinicaltrials.gov, www.controlled-trials.com). This is necessary to publish the study results in a renowned journal.

11. AMENDMENTS

After the protocol has been submitted to an ethics committee (EC), any substantial change will require a formal amendment. The amendment must be signed by all of the signatories to the original protocol. Once the study has started, amendments should be made only in exceptional cases. The ethics committees must be informed of all amendments. If necessary, approval must be sought for ethical aspects and must also be obtained from the competent authorities.
However, approval must be obtained as soon as possible after implementation. Therefore, the sponsor must inform the CA and the EC concerned of the new events, the measures taken and their plan for further action as soon as possible. The procedure is as follows: immediate telephone contact → e-mail or FAX notice → follow-up letter.

12. ETHICAL AND REGULATORY ASPECTS

12.1 Responsibilities of the sponsor and investigator(s)

The sponsor of this clinical trial will assume responsibility for inducement, organization and financing of the implementing trial according to the ICH E6. The procedures set out in this study protocol are designed to ensure that the sponsor and the Investigator comply with the principles of ICH-GCP the Declaration of Helsinki and the ICH E6 guideline concerning the conduct, evaluation and documentation of the study. The study will also be performed adhering the local legal conditions and requirements. Each Investigator has to confirm this by signing the study protocol.
Responsibilities of the sponsor:

- verification of the understanding of the investigator's brochure
- verification of the understanding of schedule
- ensuring for enough time and capacity for the implementation of this study
- correct collection and documentation of data, reporting
- provision of all data to the sponsor, or relevant authorities for audits or inspections

The principal investigator accepts the responsibility for the conduct of this clinical trial at this study site according to the ICH E6

12.2 Approval of ethics committee and notification to authority

Prior to study start, the study protocol and/or other appropriate documents will be submitted to the relevant ECs and CAs for approval. Approval from all concerned ECs and CAs must be obtained before starting the study.

12.3 Data protection and confidentiality

All local legal requirements regarding data protection will be adhered. All study findings and documents will be regarded as confidential. The Investigator and members of the research team must not disclose any information without prior written approval from the sponsor.

12.4 Financing

No financing is needed.

12.5 Regulatory aspects

The processes set out in this study protocol are designed to ensure that the sponsor and the Investigator abide the principles of the ICH E6 and the Declaration of Helsinki concerning the conduct, evaluation and documentation of the study. The study will also be performed in compliance with the local legal conditions and requirements. Each investigator has to confirm this by signing the study protocol.

13. REFERENCES

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14. APPENDICES

1. Parameters_for_CVS_treatment.xlsx
2. CVS_CRF.docx