Załącznik nr 2 do Umowy Nr ….. z dnia …….

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2. ABBREVATIONS

AE	Adverse Event
eCRF	Electronic Case Report Form
CSP	Clinical Study Protocol
CTM	Clinical Trial Manager
CV	Curriculum Vitae
DCF	Data Clarification Form
DMC	Data Management Comittee
EC	Ethics Committee
GCP	Good Clinical Practice
ICON	Informed Consent Form
ISO	International Organization for Standardization
ISF	Investigator Site File
KKS	Koordinationszentrum für Klinische Studien / Clinical Trials Coordination Centre
IMP	Investigational Medicinal Product
MV	Monitoring Visit
MVR	Monitoring Visit Report
QM	Quality Manager
RMV	Routine Monitoring Visit
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

3. SCOPE OF WORK

This monitoring plan applies to the clinical study entitled “Mesalamine for Colorectal Cancer Prevention Program in Lynch syndrome - MesaCAPP”. The trial is conducted as a multicenter, multinational trial and plans to involve 540 patients in 6 countries (Austria/Germany/Netherlands/Poland/Israel/Sweden). The sponsor of the clinical trial is the Medical University of Vienna in Austria.

In this Clinical Trial a risk-adapted Monitoring will be performed.

The monitoring plan establishes the minimum criteria for conducting monitoring visits and study related tasks and is intended to be a primary resource for clinical research associates (CRAs) monitoring the clinical study site for the duration of the study.
The monitoring plan serves as a secondary resource to other clinical trial divisions (e.g. data management).

1. APPLICABLE GUIDELINES AND DOCUMENTS

The monitoring plan should be used as a supportive guide and does not replace any standard operating procedures (SOP).
The monitoring will be conducted in accordance with the clinical study protocol, ICH/GCP, the applicable laws and guidelines and the Declaration of Helsinki.
In case of risk-adapted monitoring the risk-analysis refers to the Adamon project[1]. Knowledge of the appropriate SOPs, GCP guidelines, applicable local laws and other relevant information required to adequately carry out the tasks described in this document are assumed.

2. MONITOR OVERALL RESPONSIBILITIES & TRAINING

The Monitor will perform site management activities to ensure successful study progress. These activities may include, but are not limited to:

- Assist in training new team members as appropriate
- Initiate regular contacts with the study site and the Investigator
- Inform the sponsor of all important issues about the site performance and compliance in writing or by phone
- Contact the investigator on a regular basis to discuss study progress, important issues, adverse events, etc.
- Perform Initiation visit, Routine monitoring visits and Close out visit according to KKS SOPs
- Prior to each visit, schedule an appointment and confirm the visit in writing by involving the Investigator
- Prepare a monitoring report summarizing the items discussed during the visit and send it to both the Investigator and the Sponsor
- Perform source data verification and drug accountability
- Verify the accuracy and completeness of data reported in the CRF
- Follow up on protocol deviations
- Ensure serious adverse events are reported on time to the sponsor, the EC and BASG (Development Safety Update Report)

1
ADAMON is a project to evaluate risk-adapted monitoring strategies for clinical trials. The adapted monitoring strategies investigated have been developed with a methodology that was initially developed heuristically in preliminary projects, integrating numerous experts. Further information is described on http://www.adamon.de/ADAMON_EN/Home.aspx and in the publication of Brosteanu et al. (Clinical Trials 2009; 6: 585–596). Find the complete article on: http://ctj.sagepub.com/content/6/6/585.long

3. MONITORING

3.1 Risk-adapted monitoring

The sponsor and the KKS agreed on a risk-adapted monitoring strategy for this trial. In order to adequately estimate the appropriate amount of on-site monitoring for the trial a risk analysis as proposed by Brosteanu et al. (ADAMON project) has been conducted [Appendix 1]. The risk analysis refers to the risk of noncompliance with the main objectives of Good Clinical Practice, which are the integrity of valid data and the safety of patients.
The used risk-assessment procedure was developed and evaluated by experts from research networks (i.e. members of National Competent Authorities).
According the risk analysis the present trial can be categorized as a low-risk trial, which is mainly based on the fact that Mesalamine (5-ASA) at the proposed dose is well tolerated in clinical trials and in clinical day-to-day practice since over 30 years. There is no evidence of dose-related side effects of 5-ASA, so both tested doses shall be equally well tolerated.

Definition of Key Data and Monitoring Depth (Risk-adapted Monitoring)

The key data comprise the trial data and information that are essential to assess patient safety, well-being and rights and the compliance with the main objectives of Good Clinical Practice.
In this Clinical trial the following defined key data will be verified by the monitor within the on-site visits.

<u>The key data listed below will be verified for 100 % of all trial participants:</u>

- **Existence of the trial subject**
  A check is made to establish whether the trial subject is included in the patient identification list and whether a patient file exists in connection with any list entry.
- **Informed Consent documentation**
  A check is made to establish whether a written inform consent form exists, and whether it was filled in correctly, completely and on time.
- **Serious adverse events (SAE)**
  A check is made to establish whether all serious adverse events mentioned in the patient's file are correctly and completely documented and whether they correspond to the trial protocol specifications. Vice versa, a check is also made to establish whether source data exists in respect of all reported SAEs.
- **Primary endpoint**
  The primary endpoint(s) for the clinical trial is/are subjected to a source data verification process. This applies if the parameter(s) was/were assessed at the trial site. If the assessment is done on a centralised basis by a reference panel or institution, the monitoring activity on site referring to the primary endpoint will consist in checking whether the necessary material or the necessary information has been passed on.

100% source data verification (SDV) will only be performed for the 1st subject enrolled at the trial site.

Additionally the items listed below will be checked in a reduced manner as follows:

- **Inclusion and exclusion criteria**
  For 20% of all study subjects (randomly sampled) medical records will be carefully reviewed by the CRA to assess the eligibility of the study participants.
- **Drug Accountability/IMP Compliance**
  For 20% of all study subjects (randomly sampled) a check on the drug accountability/drug dispensing log and IMP compliance will be made at each monitoring visit.

Periodically the monitor will control the IMP accountability forms and check all IMP returns.

The total amount of on–site monitoring visits were pre-calculated in advance but will be adjusted to the defined Monitoring depth (control of key data and essential documents as well as Site personnel compliance) and therefore to the total amount of work. Any problems during the study, increased incidence of SAE, as well as other unscheduled events during the conduct of study may lead to an increase of monitoring visits and project work. In case of the consideration that there is a need to increase the monitoring visits as well as in case of Site non-compliance the responsible monitor will immediately inform the sponsor/KKS and discuss the further steps.

3.2 Initiation Visit

The general purpose of the initiation visit is to train the site staff on the procedures of the study. The agenda for the initiation of the trial site is prepared by the Monitor and discussed with the study team, in order to ensure that all trial-related procedures will be carried out according to ICH/GCP.

Prior to the Initiation visit:
The monitor shall notify the Investigator in writing (by Email or phone) to confirm the date of the visit and ensure that all staff participating in the study is available at the visit.

During the Initiation visit:
The monitor shall ensure that all relevant Site personnel signatures are obtained, including the Site visit log and the Authorization log.

The following items should be discussed with the trial site:

- Protocol:
  Review and
  - Study objectives
  - Study endpoints
  - Inclusion/exclusion criteria
  - Study design
  - Clinical and laboratory assessments
  - Study visits/procedures and interventions
  - Subject withdrawal

- Informed consent process
- Study timelines and recruitment requirements
- Regulatory obligations, including AE/SAE reporting, and EC/BASG requirements
- Investigators obligations
- Handling and storage conditions for IMP and Study material
- Archiving
- Sample storage and drug accountability

3.3 Routine Monitoring Visit

The general purpose of the Routine monitoring visit is to ensure that the clinical study is conducted according to ICH-GCP and the regulatory requirements. It is the responsibility of the sponsor to determine the extent and depth of on-site monitoring, while ensuring compliance with GCP objectives.

The routine monitoring visit will be performed in accordance with the protocol specific requirements and GCP/ICH (Good Clinical Practice/ International Council for Harmonisation).

The Monitor shall visit the site according to this monitoring plan. The frequency of the routine monitoring visits was determined by the sponsor and contains the following:

The first routine monitoring visit should take place after recruitment of the first trial subject.

The frequency of the routine monitoring visits will depend on the study time period, number of subjects enrolled, site needing extra assistance, demand for data collection, and other study management issues. The Monitor will ensure that the routine monitoring visits are conducted in a timely manner based on study site performance and in accordance with the sponsor decision.

However, an escalation of on-site monitoring visits including an increase of SDV should be considered in case of GCP non-compliance of study Site or increased number of Serious Adverse Events. In this individual case the responsible monitor will inform the sponsor/KKS immediately and may give an advice for the escalation process based on the risk evaluation.

Prior to the routine monitoring visit:
The monitor shall notify the site in writing (by Email or phone) to confirm the date of the visit and ensure that all relevant site staff is available at the visit.

During the routine monitoring visit:
Each monitoring visit at the trial site should be documented on the site visit log and be confirmed by signature by the investigator or a person authorised by the investigator.

During the screening and enrolment phase, a complete review (100%) of ICONs and the consent process (documented in the medical record) has to be performed.

All inconsistencies found during the MV (with any of the above items) must be discussed with the investigator and reported in the corresponding monitoring visit report. Site CAPA (corrective and preventive actions) items must be assigned to resolve and prevent the inconsistencies in the future.

3.4 Close out Visit

The general purpose of the close out visit is to terminate all study-related activities at the study site.

The close out visit is the final monitoring visit at the study site and will be performed after the sites last subject has completed the last visit, all data queries for the site have been resolved and the data base has been locked.

The close out visit will be performed in accordance with the protocol specific requirements in accordance to ICH-GCP (Good Clinical Practice/ International Conference on Harmonisation).

Prior to the close-out visit:
The monitor shall notify the site in writing (e.g. Email, letter or fax) to confirm the date of the visit and ensure that all relevant site staff is available at the visit.

During the close-out monitoring visit:
The site visit log has to be signed accordingly.

The following study specific issues have to be covered during the close out visit:

- Inventory and return of study supplies other than investigational medicinal products (IMP)
- Final accountability of the investigational medical product (IMP) (no IMP shall stay at site after close out visit)
- Final review of ISF including filing of essential documents and ensuring that all required documents are in place
- Retrieval of pending and finalized study documents to ensure to have the required documents available in the ISF (and in addition in the trial master file)
- Final review of site facilities and personal
- Archiving and requirements of essential document storage

The national coordinator or delegated person has to inform the EC and competent authority about study closure.

3.5 Communication and Report Documentation

The Monitor will contact the site via phone or Email between monitoring visits if needed. The purpose of these contacts is to discuss any relevant issues as identified by either the site, Monitor or clinical trial management. The discussion can include: verifying subject enrolment status, reviewing study progress, answering protocol questions, discussing CRF completion, ensuring follow-up from prior monitoring visits is completed, obtaining resolution to data queries and ensuring that the study proceeds in a timely manner.

Within 10 working days after the monitoring visit, the Monitor shall forward a monitoring report to the investigator and other persons present during the monitoring visit, briefly summarizing the activities and providing a list of action points. Critical and important findings are to be discussed with the sponsor immediately. These activities should be documented and filed appropriately.

The KKS version of the monitoring visit report template will be used to document the results of each visit. A visit report has to be prepared and send to the sponsor after each visit. The original of the final visit report is to be filed in the TMF. A copy of the report remains at the KKS.

The initiation visit report should clearly document that the site agrees to comply with the CSP (Clinical Study Protocol). The responsible Monitor should document, that the AE/SAE (AMG) or AE/SAE reporting procedures, investigators obligations, the process for obtaining informed consent and source data documentation were reviewed and understood by the investigator. Verbalized or observed non-compliance or non-agreement to the protocol should be reported as an issue item on the monitoring report.

In case the statistician gets the completed CRF data handed out by KKS, the clinical trial manager of KKS should stay in contact after transmission the data, regarding the status of analysis and queries. A dispatch form will be completed and filed in the TMF.

3.6 Source Data Verification

Source data verification (SDV) is the verification of source document data compared to the data recorded in the CRF. Source documents are considered to be original documents that report tests and results, consultations or examinations of a trial subject. Source document worksheets may be developed and prepared by site staff in aim to collect required source data. These are not mandatory to be used by the site, but recommended.
Generated print-outs are considered as source data if signed by the Investigator. Furthermore, these print-outs will be collected in the CRFs.

During all phases of the trial, the Monitor reviews the CRF entries against source documents.

For **screening failure-subjects** only the signed informed consent form and reason for failure has to be reviewed.

3.7 Note to File

File notes are separate documents to be used in cases where the situation cannot be described in a different manner and a Protocol deviation form is not applicable.
File notes can either refer to a trial subject, trial site or be of general character.

They should contain a brief description of the issue and describe the reasons / solutions / measures of current or future procedures. File notes must be signed and dated by Investigator.

4. ISSUE MANAGEMENT

4.1 Issue Identification and Management / Escalation Process

A critical issue is any issue that significantly affects subject safety, study efficacy, data integrity or study conduct according ICH-GCP.

The Monitor will communicate critical site issues to the sponsor as soon as possible, or immediately if subject safety is involved.

Each critical issue will be handled individually and as discussed with the Sponsor.

4.2 Handling Protocol Deviations and Violations

The investigator may deviate from the CSP without prior approval only when it is necessary to eliminate an apparent immediate hazard to the subject.

During monitoring visits the Monitor will document observed protocol deviations on a separate **protocol deviation form** provided and approved by the KKS. This form is then handed over to the sponsor for notification and further decisions (e.g. premature patient exclusion). The Monitor shall verify that all protocol deviations have been documented and commented in the CRF accordingly. Additionally all observed protocol deviations will be mentioned in a designated section of the Monitoring report.

In addition, the Monitor will discuss these deviations in person with the investigator or other responsible site personnel and re-educate the site as appropriate. The discussion and training should also be documented in the MVR. Problems and protocol deviations at a trial site mentioned in the MVR should be revised by the Monitor during the next monitoring visit in order to approve clarification of the remaining points.

4.3 Scientific Misconduct and Fraud

Fraud is the intention to deceive. Misconduct is serious non-compliance defined as failure to adhere to the relevant regulatory requirements to the extent that patient safety has been put at risk or where non-compliance results in a breach of medical ethical standards. Also included is any breach in data integrity.

The Monitor is responsible for reporting all suspected cases of fraud or misconduct in clinical research to the sponsor immediately.

5. PROJECT SPECIFIC PROCEDURES

5.1 (S)AE Reporting

At each routine monitoring visit, the Monitor has to review all available source data to ensure that all AEs have been recognized and reported.

The investigator or authorized physician have to assess all AEs to causality (not related/ unlikely/ possibly related/ probably related/ related / not assessable to the investigational product), severity (mild / moderate / severe) and seriousness (non-serious / serious). If the KKS has the contractual commitment, the sponsor should be informed about cases of serious adverse events.

In case copies of hospital records or other supportive AE documentation have to be forwarded to the sponsor, the personal data of the subject have to be anonymised.

Non-serious Adverse Events
The Monitor must ensure that all non-serious AEs appearing in the source documentation are properly captured on the AE pages of the CRF.

Ongoing AEs will be followed-up until resolved or medically stabilized, or until the subjects study termination.

Serious Adverse Events
SAE reporting will be conducted according to the corresponding **KKS template**.

If an unreported SAE is discovered during a routine monitoring visit, the Monitor will facilitate the completion of the SAE report form and ensure immediate forwarding.

The Monitor has to verify that all SAEs have been followed-up until resolved or medically stabilized. All changes on the original SAE report form require initialing and dating of the corrected/added data and re-signature at the end of the report.

5.2 Pregnancy

All pregnancies occurring during the study must be reported by the investigator immediately upon becoming aware of the event by faxing the “Pregnancy Report Form” analogously to the procedure described for SAE reporting in section 6.1.
In case a SAE is related to the pregnancy, a SAE report has to be completed additionally to the pregnancy report.

5.3 Obtaining Informed Consent Process

Upon site initiation, the Monitor has to train the investigator on the informed consent process and obtain the investigator’s signature on the respective training log.

The investigator will explain in simple language the nature and scope of the study as well as potential risks and benefits of participation to the subject. The investigator will answer the subject's questions. Informed written consent must be obtained from each subject prior to any study-related intervention being performed.
It is important that the subject has sufficient time to decide on participation in the study. Neither the investigator nor the study staff should influence the subject to participate. The subject has to sign AND date the ICON personally and will receive a signed copy. With their dated signature on the Informed consent form the subject is considered as enrolled.

The Monitor will verify that the process of obtaining informed consent has been conducted and documented according to all applicable regulatory requirements and the local EC requirements.

The Monitor shall document the check of the ICON and report any failure to comply with the requirements in the MVR. Any serious deviation/non-compliance in the informed consent process will be discussed with site and reported to the sponsor.

In case any new information becomes available that significantly bears on the subject, this will be communicated by the investigator to the subject, who has to consider further participation and, if applicable, sign and date the updated ICON.

6. RANDOMIZATION

For randomization the web-program "randomizer" at the Medical University of Vienna will be used (https://www.meduniwien.ac.at/randomizer). Patients will be stratified by country and history of previous CRC. Patients will be randomized in 1:1:1 ratio on Day 0 of the treatment period to one of the 2 dose groups or placebo by minimization method. An email confirmation of randomization is sent to site and should be considered as source document. Every randomized patient receives a randomization number. According to this number blinded medication is provided to the patients.

6.1 Investigational Medical Product Logistics, Handling and Accountability

Study drug delivery will be done by pharmacy Heidelberg to the coordinating investigators. For Germany, IMP will be delivered to the study sites directly. IMP has to be stored in original package at max. 25°C.
IMP will be labeled, packaged and delivered to sites by pharmacy Heidelberg.
The labeling and packaging will be done according to local legal requirements and GMP.

- **IMP Administration & Handling**
  Patient should be at least 75% compliant with the IMP. If the patient takes less than 75% IMP or uses more than 25% additional IMP the investigator hast to train the patient on protocol specific medication intake. The training should be documented in patient source documents. In case of regular incompliance patient should be withdrawn from IMP intake after investigator's judgement.
  At site visits the empty containers will be exchanged with new medication supply.

- **Drug Accountability**
  - The investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of drug records.

  - Upon receipt of IMP the investigator or designated site staff will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by the pharmacy Heidelberg. A copy of each document will be filed in the Trial Master File and another copy will be retained for the Investigator Site File.

  - The dispensing of the IMP will be carefully recorded at the site on the appropriate drug accountability forms and an accurate accounting will be available for verification by the monitor.

  - IMP accountability records will include:
    - Confirmation of IMP delivery to the trial site
    - The inventory of IMP at the site provided by the sponsor
    - The use of each dose by each subject, documented in the patient diary
    - Randomization confirmation
    - The return or alternative disposition of unused IMP
    - Dates, quantities, batch numbers, expiry dates and the patient IDs assigned

  - The investigator should maintain records which adequately document that:
    - The IMP was provided to the subjects in the doses specified by the protocol/amendment(s) and randomization
    - All IMP provided by the pharmacy Heidelberg were fully reconciled

IMP which has been dispensed to a subject must not be re-dispensed to a different subject. Unused IMP must not be discarded or used for any purpose other than the present trial. All medication and containers will be returned to the pharmacy Heidelberg.
The monitor will control the IMP accountability forms and check IMP returns as described in section 3.1.

Address pharmacy Heidelberg:
Apotheke des Universitätsklinikums Heidelberg
Im Neuenheimer Feld 670
69120 Heidelberg
Responsible pharmacist:
Dr. Lenka Taylor
Email: lenka.taylor@med.uni-heidelberg.de

7. CRF INSTRUCTIONS

7.1 General

An electronic CRF (eCRF) will be used for data collection.

No data will be retrieved for **screening failure-subjects** (no data entered in the eCRF). The reason for failure will be documented in source data, screening log, and MVR.

The Monitor must check each eCRF page for completeness, correctness and consistency with the available source data.
The Monitor has to communicate closely with the site to ensure timely data entry and query resolution in order to meet the study timelines.

If the quality of the CRF completion is inadequate this should be discussed with the investigator and/or the appropriate site staff. Details of the discussion should be documented in the monitoring visit report until resolved.

In case of incorrect or incomplete entries, the Monitor has to make sure that appropriate corrections, additions, or deletions are made, explained (if necessary), initialled and dated by authorized site personnel. Corrections to the original CRFs are made in such a way as to leave the original entry legible.

Corrections to original completed CRFs should be made by the investigator. Sub-Investigators or other study personnel may also do corrections, if they are authorized by the Investigator by date and signature on the Authorization log.

7.2 Query Management

The monitor and KKS data management can create queries via direct eCRF entry, which will be electronically transferred to the assigned person at the study site personnel.
The queries have to be resolved as soon as possible, latest at the next monitoring visit. The monitor has to check if the answer is consistent with source data. In case of Site non-compliance the monitor will immediately inform the sponsor / KKS and discuss the further steps.

After data export and electronic data transfer to the sponsor the Monitor should be informed about all queries or discrepancies that may be detected by the sponsor/statistician. The communication with the Investigator lies with the sponsor. The monitor will be involved for any situational decisions by the sponsor.

7.3 Collecting and Forwarding CRF

In case no other agreement has taken place, the monitor locks completed and verified eCRFs during the close out visit. The data management will then export data from the eCRFs and transfer them to an electronic media. One copy will remain at the site another copy will be forwarded to the sponsor for TMF filing. It is the responsibility of the Investigator to archive copies of eCRF.

After the study was completed and the database is locked, the data is downloaded and stored on a CD/DVD. The CD/DVD will be sent by the CTM to sponsor for archiving.