CONFIDENTIAL

CLINICAL STUDY PROTOCOL

for 5,6 or 7 year follow-up control after the SCHEDULE study

(SCANDINAVIAN HEART TRANSPLANT EVEROLIMUS DE NOVO STUDY WITH EARLY CNI AVOIDANCE)

Study code:	CRAD001ANO05 / NCT02864706
EudraCT number:	2016-000404-28
Version number:	FINAL 2.0-DK
Development phase:	IV
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Document history:	This version of the Clinical Study Protocol includes: • Substantial Amendment No.1, FINAL 1.0, 27-Jun-2016 • Updates to Section 4.5 as requested by the Danish Health Authority during the assessment of the CTA

Title of original SCHEDULE study:

A controlled randomized open-label multicentre study evaluating if early initiation of everolimus (Certican®) and early elimination of cyclosporine (Sandimmun Neoral®) in de novo heart transplant recipients can improve long-term renal function and slow down the progression of chronic allograft vasculopathy.

Study code:	CRAD001ANO02
EudraCT number:	2009-013074-41

Coordinating Investigator:	[redacted]
Sponsor Signatory:	[redacted]

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REASON AND RATIONALE FOR THE FOLLOW-UP CONTROL

This protocol is written to describe the procedures for a single 5, 6 or 7 year follow-up control visit of patients that participated in the 12-month SCHEDULE-study and the following 3-year follow-up examiniation/visit. The aim of this 5 to 7-year follow-up visit is to examine the effect of long term treatment, i.e. 5, 6 or 7 years, with early initiation of everolimus (Certican®) and early elimination of cyclosporine (CsA), compared to standard immunosuppressive regimen including CsA, on renal and heart function. During the time period of this follow-up examinations this visit will be performed as part of a routine annual visit 5, 6 or 7 years since transplantation (and inclusion in the original SCHEDULE study).

PROTOCOL FOR THE 5 TO 7-YEAR FOLLOW-UP EXAMINATION

1 INTRODUCTION

1.1 Background

The calcineurin inhibitors (CNIs) have contributed to low acute rejection rates and favourable short-term graft survival in heart transplantation (HTx) with 80-90% patients survival after 12 months. However, the protective role of these and other immunosuppressive drugs in the development of cardiac allograft vasculopathy is uncertain; in fact CNIs and steroids have been implicated in the pathological development of this condition. In addition, new long term adverse effects have occurred including CNI-induced nephrotoxicity. Nearly 30% of HTx recipients demonstrate renal dysfunction already at 1 year post-HTx. Importantly, a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 at this time point has been shown by our own group to be an independent risk factor for both all-cause and cardiac mortality (1).

Everolimus, a proliferation signal inhibitor (PSI) is a potent, rapamycin-related immunosuppressive agent that exerts its immunosuppressive effect by blocking interleukin (IL-2 and IL-5) driven proliferation of T and B cells. PSIs do not share the nephrotoxic properties of CNIs, but potential serious side effects such as exacerbation of proteinuria, impaired wound healing and pulmonary inflammation have been reported.

As attention shifts towards improving long-term outcomes in thoracic transplant recipients, there is a growing emphasis on maintenance immunosuppressive regimens that minimize exposure to CNIs (2). CNI-related renal toxicity (3) is of particular concern in view of the high rate of chronic renal failure observed in heart and lung transplant recipients (4), but other CNI-related complications such as diabetes mellitus, hyperlipidemia, hypertension and infections can also adversely affect outcomes. Importantly, progressive renal disease, metabolic abnormalities and infections contribute to the risk of cardiac allograft vasculopathy (CAV) (5), the leading cause of death after the first year following HTx (6). Rapid progression of CAV in the first 5 years as well as in the first year after transplantation detected by intravascular ultrasound (IVUS) analysis is a powerful predictor for mortality, myocardial infarction, and the development of angiographic abnormalities (7, 8).

The introduction of PSIs has created a novel opportunity to limit CNI exposure without loss of efficacy.

Follow-up Examinations

Extension phase of important studies are not uncommon, including in transplantation studies. Data of this kind have been published from other large outcome HTx studies (9, 10, 11). This form of studies allows a more complete evaluation of the effect of treatment as well as side effects.

The results from the SCHEDULE 3-year follow-up visit indicated that the beneficial effect of everolimus treatment with early CNI withdrawal on renal function in *de novo* heart transplant recipients seen at 12 months after transplantation (12) was maintained at 3 years after transplantation (13). The aim of this 5 to 7-year follow-up visit is therefore to further examine the long term effect (i.e. 5 to 7-years) of the combination of everolimus followed by early Cyclosporine A (CsA) withdrawal compared to standard immunosuppressive regimen including CsA, on renal function and progression of CAV.

1.2 Study Purpose

To evaluate, in *de novo* heart transplant recipients, whether early initiation of everolimus and early elimination of CsA compared to standard immunosuppressive regimen including CsA can improve long-term renal function and slow down the progression of CAV.

2 AIMS/OBJECTIVES

The major aim of this extension study is to evaluate the long-term (i.e. 5 to 7 years) effect of early initiation of everolimus and early elimination of CsA compared to standard immunosuppressive regimen including CsA on primary and secondary endpoints investigated in the SCHEDULE main study. The endpoints for this 5 to 7-year follow-up visit are:

Primary endpoint:

- Renal function as assessed by measured glomerular filtration rate (mGFR)

Secondary endpoints:

- Progression of CAV by IVUS analysis
- Myocardial structure and function by echocardiography assessment
- Quality of life by SF-36 (Minnesota Living with Heart Failure Questionnaire), Euro Quality of Life 5D (EQ 5D), and Beck Depression Inventory (BDI) form
- Number of adverse events (AEs)/serious adverse events (SAEs)

3 STUDY DESIGN

The 12-months SCHEDULE main study was a prospective, multi-center, randomized, controlled, parallel group, open label study in *de novo* heart transplant recipients. The study consisted of two study periods, period 1 (HTx to week 7-11) and period 2 (week 7-11 to Month 12). Patients fulfilling the inclusion and exclusion criteria were randomized to one of two treatment groups: (i) conventional treatment with CsA, mycophenolate mofetil (MMF), and corticosteroids (Group A), or (ii) low-dose CsA, everolimus, MMF, and corticosteroids (Group B). After period 1, CsA was discontinued in Group B (experimental set-up with off-label use of everolimus), while the standard triple-drug immunosuppressive regimen was maintained in Group A.

In the 12-month SCHEDULE-study, 115 patients were randomized and treated. The main study was followed by a 3-year follow-up visit in which 102 of the 115 patients participated.

This 5 to 7-year follow-up visit is a further longtime follow-up examination of the patients participating in the SCHEDULE main study and the 3-year follow-up visit.

4 MATERIAL AND METHODS

4.1 Patients

Inclusion criteria:

- Patients who participated in the SCHEDULE 12-month main study, and who completed the 3 year follow-up visit,
- Patients who are coming for a regular annual clinic visit 5 to 7 years after randomization in the main study
- Obtaining of a separate signed patient informed consent will be required for participation in this follow-up examination.

Exclusion criterium:

- Patients with a retransplanted heart since the original SCHEDULE study

The patients will be allocated the same patient number as in the main study. The patients were recruited from six transplant centers in Norway, Sweden and Denmark. Since this is a single visit control there are no withdrawal criteria.

4.2 Treatments

After randomization in the main study patients in Group A received an immunosuppressive regimen consisting of CsA, MMF and corticosteroids in both study periods. Patients in Group B commenced on an immunosuppressive regimen consisting of low dose everolimus and CsA, MMF and corticosteroids in period 1. In period 2 the patients were subjected to abrupt and complete CNI withdrawal, to a CNI free immunosuppressive regimen consisting of everolimus, MMF and corticosteroids.

After completion of the main study (12-months), most of the patients continued on the same immunosuppression. However, patients might have switched to alternative immunosuppressive drugs between Month 12 in the main study, the 3-year follow-up visit, and the 5 to 7-year follow-up visit.

4.3 Efficacy assessments

The assessments to be performed at the 5 to 7-year follow-up visit are presented in Table 1. The same clinical methods/investigations as used for the 12-month assessments (Visit 11) and the 3-year follow-up visit will be used at the 5 to 7-year follow-up visit. Data from the main study and from the 3 year follow-up visit will also be used.

- **Table 1 Assessment Schedule**

Visit	Follow-up
Time after randomization	**5 to 7 years**
Informed consent	X
Baseline data	X
Concomitant therapy	X
Immunosuppressive therapy	X
12-led ECG	X
Vital signs	X
Echocardiography	X
Quality of life	X
IVUS[1,2]	X
Laboratory test hematology/biochemistry[3]	X
Laboratory test/lipid profile[4]	X
Urinalysis[5]	X
[redacted]	[redacted]
mGFR	X
Drug concentration trough levels:	
CsA	X
Tacrolimus	X
Everolimus	X
Drug daily doses:	
CsA	X
Tacrolimus	X
Everolimus	X
Corticosteroids	X
MMF	X
AEs	X
SAEs	X

ECG, electrocardiogram; IVUS, intravascular ultrasound; [redacted]; mGFR, measured glomerular filtration rate; CsA, cyclosporine; MMF, mycophenolate mofetil; AEs, adverse events; SAEs, serious adverse events

1. Measurements of microcirculation to be performed in connection with routine coronary angiography prior to IVUS examination (optional)
2. If IVUS is not performed as part of the assessments made at the follow-up study visit 5 or 6 years after transplantation IVUS may be collected at the subsequent regular annual routine visit
3. Hematology: hemoglobin, leukocytes, thrombocytes. Biochemistry: ASAT, ALAT, Urea, Creatinine, Uric acid, Sodium, Potassium, Albumin
4. Laboratory tests/Lipid profile: Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HbA1c, NT-proBNP, Troponin T, CRP
5. Urinalysis: Albumin/creatinine ratio

4.3.1 Baseline Data for the Follow-up Visit

The following demographic/baseline data will be collected at the follow-up visit:

- Patient number (randomization number in the main study)
- Date of visit
- Patient informed consent (date of obtained ICF) or the reason for not giving consent (i.e. death, patient unwilling to give consent, other reason)

4.3.2 Immunosuppressive Medication and Other Concomitant Medications

Present (at the time of the 5 to 7-year follow-up visit) immunosuppressive treatment (everolimus, CsA/tacrolimus, MMF, and corticosteroids [i.e. prednisolone]) including daily dose, information on start and/or stop of immunosuppressive treatment since the end of the original study and reasons for stopping/starting the immunosuppressive drugs will be collected. Present concomitant medications including indication and route of administration will also be collected.

4.3.3 Renal Function

Measured Glomerular Filtration Rate

Renal function will be assessed by mGFR using the same method as used in the main study (chrome-Ethylenediaminetetraacetic acid [Cr-EDTA] clearance, technetium ^{99}m-Diethylenetriaminepentaacetic acid [^{99m}Tc-DTPA] clearance, or Iohexol clearance).

[redacted]

Urine Spot Sample

A spot sample (dipstick) will be used for determination of proteinuria (albumin/creatinine ratio).

4.3.4 Intravascular Ultrasound and Cardiac Function

Intravascular Ultrasound Measurements

Intravascular ultrasound (IVUS) will only be performed on patients who have done IVUS examinations in the main study and at the 3-year follow-up visit.

Note: If IVUS is not performed as part of the assessments made at the follow-up study visit 5 or 6 years after transplantation IVUS may be collected at the subsequent regular annual routine visit.

IVUS recordings will be performed in connection with a routine left sided heart catheterization using special catheters. Semi-automated contour detection of both the lumen and external elastic membrane (EEM) will be performed at intervals of 60 frames using dedicated software (QIVUS Clinical Edition, Medis Medical Imaging, Leiden, Netherlands). The longest possible segment between the most distal and proximal side branch visualized in the IVUS pullback will be analyzed for each patient. Following automatic contour detection, borders will be edited manually by two independent operators according to the guidelines for acquisition and analysis of IVUS images by the American College of Cardiology and European Society of Cardiology.

The following parameters will be recorded for all patients using the mean result of all frames analyzed:

- lumen cross-sectional area (CSA)
- vessel CSA
- intimal CSA
- maximal intimal thickness (MIT)

The CSA measurements will be utilized to calculate total atheroma volume using Simpson's method, as well as percent atheroma volume (PAV). The PAV value will be used for defining CAV.

Echocardiography

Standard echocardiography assessment as done in the main study will be performed.

Patients will be examined in the lateral recumbent position after 15 minutes of rest. The heart will be visualized by standard ultrasonic techniques and acoustic windows giving a total homodynamic and valvular assessment.

Three heartbeats will be needed for this analysis. Analysis will be done blinded. Standard measurements including left ventricular end systolic dimension (LVESD) and left ventricular end diastolic dimension (LVEDD), , left ventricular performance assessed as fractional shortening (FF%), and left ventricular ejection fraction (LVEF) (Simpson's method) will be performed. Local echocardiographic recordings will be recorded, echocardiographic recordings may also be read centrally.

4.3.5 Vital Signs

Body weight (kg), height (cm), systolic and diastolic blood pressure (mmHg; seated after at least 20 minutes of rest), and heart rate (beats/min) will be recorded.

4.3.6 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed, and the following ECG parameters will be documented: type of rhythm, heart rate, PQ time, and QRS interval.

4.3.7 Cardiac rejections

Number and grading of biopsy proven and treated rejections and rejections with hemodynamic compromize since the 3 year follow-up visit will be collected.

4.3.8 Laboratory Evaluations

Hematology, Biochemistry and Urinalysis

The following laboratory parameters will be analyzed:

Hematology: hemoglobin, leukocytes, platelets.

Biochemistry: serum creatinine, urea, uric acid, sodium, potassium, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), albumin.

Lipid profile/laboratory tests: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HbA1c, NT-proBNP, Troponin T, C-reactive protein (CRP).

Urinalysis: albumin/creatinine ratio, see Section 4.3.3.

Drug Concentration Trough Levels

Whole blood levels (C-0 levels) will be measured for everolimus, CsA, and tacrolimus as part of the routine laboratory measurements.

4.3.9 Health-related Quality of Life

Quality of life will be examined using three validated questionnaires, i.e. the SF-36, EQ 5D, and the BDI form.

4.4 Statistics

The primary efficacy analysis will be based on the intention-to-treat (ITT) population. Statistical hypothesis testing will be performed, and confidence interval (CI) will be derived to estimate the effects. Two-sided tests will be performed on the 5% level of significance, and 95% two-sided CI for least square mean will be presented.

The null hypothesis is that there is no difference in the mean of mGFR between the everolimus arm ($\mu_{Everolimus}$) and the control arm (Control) ($\mu_{Control}$) and the alternative hypothesis is that there is a difference between everolimus and control at the 5 to 7-years follow-up visit.

H_0: $\mu_{Everolimus} - \mu_{Control} = 0$

H_1: $\mu_{Everolimus} - \mu_{Control} \neq 0$

The above between-group comparisons will be performed using an ANCOVA with study treatment (Everolimus, Control) and randomization strata (mGFR above/below 60 mL/min and have/not have mechanical assist device) as classification variables. In addition, the mGFR values at baseline (Visit 6) will be used as covariate.

In general data will be summarised by means of summary statistics. For continuous data, the following summary statistics will be presented: number of observations, mean value, standard deviation, minimum, first quartile, median, third quartile and maximum value. Categorical data will be presented as counts and percentages. Summary statistics will be presented by treatment group/total and assessment visit, as applicable. Individual patient data will be listed.

The analyses of the data from the 5 to 7-year follow-up visit will be presented in a statistical analysis plan (SAP) prepared prior to database lock.

Data sets to be analysed:

The Safety Set will consist of patients who:

- were included in the Safety Set in the Clinical Study Reports Addendum dated 11 August 2015 for the 3 year follow-up visit
- have at least one assessment at the 5 to 7-year follow-up visit

The Intention-to-Treat (ITT) set will consist of patients who:

- were included in the ITT in the Clinical Study Reports Addendum dated 11 August 2015 for the 3 year follow-up visit
- have at least assessment of the efficacy variable mGFR [redacted] at the 5 to 7-year follow-up visit

The Per Protocol Set (PPS) will consist of patients who:

- were included in the PPS in the Clinical Study Reports Addendum dated 11 August 2015 for the 3 year follow-up visit
- have at least assessment of the efficacy variable mGFR [redacted] at the 5 to 7-year follow-up visit
- are on their randomized treatment i.e. Everolimus or Control (Control=Cyclosporine and/or Tacrolimus) at the 5 to 7-year follow-up visit
- have no major protocol deviation at the 5 to 7-year follow-up visit. The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol deviations are available and will be documented in a separate document before database lock

The Extended PPS will consist of patients who:

- were included in the ITT in the Clinical Study Reports Addendum dated 11 August 2015 for the 3 year follow-up visit
- have at least assessment of the efficacy variable mGFR [redacted] at the 5 to 7-year follow-up visit
- are on their randomized treatment i.e. Everolimus (Everolimus=Everolimus or Everolimus and Cyclosporine and/or Tacrolimus) or Control (Control=Cyclosporine and/or Tacrolimus [and not Everolimus]) at the 5 to 7-year follow-up visit
- have no major protocol deviation at the 5 to 7-year follow-up visit. The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol deviations are available and will be documented in a separate document before database lock

4.5 Adverse Events

4.5.1 Definitions

Adverse Event

Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment: All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorized IMP or SmPC for an authorized product).

Comments: When the outcome of an adverse reaction in this study is not consistent with the applicable product information, i.e. Section 4.8 of the SmPC, this adverse reaction should be considered as unexpected.

Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Comments: Life-threatening in the definition of a serious adverse event (SAE) or serious adverse reaction refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in

death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

4.5.2 Occurrence of Selected Adverse Events (Including Serious Adverse Events) – Main Categories

AEs considered clinically relevant are listed in Table 2. Any of these AEs that have occurred during the time between the 3-year follow-up visit and the 5 to 7-year follow-up visit should be registered in the case report form (CRF).

All SAEs should be reported to Novartis on specific SAE forms within 24 hours of learning of its occurrence to:

Clinical Safety Desk Fax:

[redacted]

To be answered: Has there been any occurrences of (clinically relevant) AEs since the 3-year follow-up visit i.e. from the 3-year follow-up visit to the 5 to 7-year follow-up visit.
The total number of each AE/SAE should be recorded, i.e. one patient may have experienced several AEs. Further details regarding collection and handling of AEs/SAEs are provided in Appendix 1.

- **Table 2 Selected Adverse Events – Main Categories**

Adverse Event	**3 years to 5/7 years**	
	AE	**SAE**
Infection		
Pneumonia		
Herpes Zoster		
Herpes simplex		
Sepsis		
Cancer		
Squamous cell carcinoma		
Basal cell carcinoma		
Other skin cancer		
PTLD		
Solid tumor		
Bone marrow toxicity		
Thrombocytopenia (<100000/µL)		
Leucopenia (<3500/µL)		
Anemia (<10 g/dL)		
Tromboembolic event		
DVT		
Pulmonary emboli		
Stroke/TIA		
Gastrointestinal system		
Diarrhea		
Constipation		
Pain		
Skin		
Rash		
Acne		
Hirsutism		
Cardiac		
Cellular rejection (grade)		
Humoral rejection		
LV dysfunction (EF<30%, or 25%↓)		
Arrhythmias (clinically significant, requiring treatment)		
PCI		
Myocardial infarction		

Adverse Event	3 years to 5/7 years	
	AE	SAE
Renal		
Proteinuria (albumin/creatinine >100)		
Hyperuricemia		
Peripheral oedema		
Gingival hyperplasia		
Other		

4.5.3 Instructions for collecting and reporting Adverse Events and Serious Adverse Events

The purpose of this instruction is to guide how to collect and handle the side effects from a practical point of view.

- When the patient comes to the clinic visit, ask him/her if there have been any adverse events (clinically relevant) since the 3-year follow-up visit (i.e. between the 3-year follow-up visit and the 5 to 7-year follow-up visit).
- Record serious and non-serious AEs and the total number of each event in the CRF (each patient might have experienced several events).
- Check the adverse events/serious adverse events against medical records in order to source verify the events.
- The serious adverse events must be reported to Novartis within 24 hours of learning of its occurrence.
- State in the medical record for the study visit:
  - that the patient has been asked for clinically relevant adverse events
  - the events reported by the patient
  - refer to where in the medical record the different adverse events can be found (e.g. by date).
- If the reported adverse events cannot be verified in medical record/any other source document the patient should be asked if he/she has been in contact with a doctor/hospital and/or received treatment due to the event and attempt to retrieve this information from the treating physician/hospital. It is important to make an effort to find the medical records/source documents and to document this for the study visit in the medical records.
- As for the original study (CRAD001NO02, EudraCT number 2009-013074-41), everolimus (Certican®) is defined as the study drug. If the SAE is not previously documented in the IB or Package Insert for (new occurrence) and is thought to be related to the study drug a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

4.5.4 Pregnancy

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department.

5. SITE MONITORING

Formal site monitoring will be performed as described in the Monitoring Plan for this study. Novartis designated CRO will assure compliance monitoring

During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the paper CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrollment. Key trial personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file which will be documented as being the source data. The investigator must also keep a copy of the signed informed consent form.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

Access to source documents by auditors and regulatory inspectors will be granted.

6. ETHICS AND GOOD CLINICAL PRACTICe

This study was planned and shall be performed according to the principles of Good Clinical Practice, the declaration of Helsinki, and national laws and regulations about clinical studies. The study will not start without written Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

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SIGNATURES

This Clinical Study Protocol is approved by:

SPONSOR'S REPRESENTATIVE:

DATE: _____

[redacted]

DATE: _____

[redacted]

COORDINATING INVESTIGATOR:

DATE: _____

[redacted]

CLINICAL STUDY PROTOCOL AGREEMENT FORM

I have read the Clinical Study Protocol, Final version 2.0-DK, dated 07-Jul-2016, and I agree to conduct the study according to this study protocol.

Principal Investigator: _____

Date: _____

Signature: _____