ReGenHeart Kick-off Meeting
Wienna 22.05.2017

Clinical Trial Protocol

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STUDY PROTOCOL

CLINICAL STUDY PROTOCOL

Study title:	**Clinical development and proof of principle testing of new regenerative VEGF-D therapy for cost-effective treatment of refractory angina** **A phase II randomized, double-blinded, placebo-controlled study**
Acronym:	**ReGenHeart**
EudraCT number	**2017-000789-31**
CT Gov number	**NCT03039751**
Study Code	**RGH201**
Study Phase:	**Phase II**
Date of protocol:	**06/03/2017**

STUDY TITLE

BRIEF TITLE

Adenovirus Vascular Endothelial Growth Factor D (AdvVEGF-D) Therapy for Treatment of Refractory Angina Pectoris (ReGenHeart)

OFFICIAL TITLE

Clinical Development and Proof of Principle Testing of New Regenerative Adenovirus Vascular Endothelial Growth Factor (VEGF-D) Therapy for Cost-effective Treatment of Refractory Angina. A Phase II Randomized, Double-blinded, Placebo-controlled Study (ReGenHeart

SUMMARY

BRIEF SUMMARY

The purpose of the study is to evaluate the **safety and efficacy** of catheter mediated endocardial adenovirus-mediated vascular endothelial growth factor-D (AdVEGF-D) regenerative gene transfer in patients with refractory angina to whom revascularisation cannot be performed.

OBJECTIVES

PRIMARY OUTCOME MEASURES

1. Functional capacity at 6 months
Improvement of exercise capacity 6 months after the treatment as measured by 6 minute walking test (walking distance in meters)

2. Severity of angina pectoris symptoms at 6 months
Relieve of angina symptoms 6 months after the treatment (CCS class)

OBJECTIVES

SECONDARY OUTCOME MEASURES (1)

Functional capacity at 12 months
Improvement of exercise capacity 12 months after the treatment as measured by a 6 minute walking test (walking distance in meters)

Severity of angina pectoris symptoms at 12 months
Relieve of angina symptoms 12 months after the treatment (CCS class)

Myocardial perfusion at 6 months
Improvement of myocardial perfusion (myocardial perfusion reserve, MPR) at 6 months assessed with positron emission tomography (PET) or single-photon emission computed tomography (SPECT)

Quality of Life (EQ-5, SF-36, SAQ) at 6 and 12 months
Improvement of QoL assessed with EQ-5, SF-36 and Seattle Angina Questionnaire at 6 and 12 months

OBJECTIVES

SECONDARY OUTCOME MEASURES (2)

Angina pectoris medication at 6 and 12 months
Use of short-acting nitrates to relieve symptoms of angina pectoris at 6 and 12 months (number of oral/sublingual nitrate tablets or nitrate spray inhalations during the preceding 4 weeks).

Adverse cardiac events at 6 and 12 months
Incidence of cardiovascular death, myocardial infarction, stroke, revascularization or hospital admission due to coronary artery disease

A combined endpoint of Major Adverse Cardiac Events MACE (combined endpoint of cardiovascular death, myocardial infarction, stroke, revascularization or hospital admission due to coronary artery disease) at 6 and 12 months.

INCLUSION CRITERIA

- informed consent signed
- age > 30 but < 85 years
- significant angina pectoris (CCS 2-3) despite of optimal medication
- significant stenosis (> 60%) in coronary angiography (< 6 months)
- contraindication to CABG or PCI due to
    - diffuse or distal stenosis,
    - chronic total occlusion,
    - vessels with difficult anatomy,
    - stenosis with severe calcifications and
    - stenosis in small vessels (<2.5 mm))
- angina pectoris or equivalent symptoms in the 6-minute walking test
- left ventricle wall > 8 mm detected by
    - transthoracic echocardiography or
    - magnetic resonance imaging (treatment area)

EXCLUSION CRITERIA

- women in fertile age
- diabetes mellitus with severe complications such as
  - diabetic retinopathy or
  - nephropathy
- clinically significant anemia
  - Hb < 120 mg/l in male, < 110 mg/l in female, hematocrit < 0.36),
- leukopenia (b-leukocyte < 3.0x109/l)
- leukocytosis (b-leukocyte > 12.0x109/l) or
- thrombocytopenia (b-thrombocyte < 100x109/l)
- renal insufficiency (P-creatinine > 160 mg/l)
- liver insufficiency (P-ALAT or P-AFOS over 2 x normal)
- haematuria of unknown origin
- severe hypertension or hypotension
  - systolic blood pressure > 200 mmHg or
  - diastolic blood pressure > 110 mmHg or
  - systolic blood pressure < 90 mmHg)

EXCLUSION CRITERIA

- significant obesity (Body Mass Index > 35)
- acute infection
- immunosuppressive medication
- significant impairment of left ventricular function (LVEF< 25% in TTE)
- symptomatic congestive heart failure (NYHA class 3-4)
- haemodynamically significant (grade 3-4/4)
    - aortic regurgitation or
    - mitral regurgitation or
    - other heart disease needing surgery
- recent (< 6 weeks)
    - acute coronary syndrome or
    - myocardial infarction,
    - PCI or
    - CABG,
    - stroke or transient ischemic attack (TIA)
- current or suspected malignancy

FLOW CHART

EVENT	Screening visit	Admission	Gene transfer	4 hours after gene transfer	Cardiac ward	Visit d14	Visit d180	Visit d360	Visits y2 and y5
TIME		day -1	day 0	day 0	day 1	day 14 +/- 2 days	day 180 +/- 30 days	day 360 +/- 30 days	year 2/ 5 +/- 1 month
1. Date of visit	X	X	X		X	X	X	X	X
2. Informed consent	X								
3. Subject information	X								
4. CV history	X								
5. CV risk factors	X								
6. CV medication	X	X			X		X	X	X
7. Other medical history and concomitant diseases	X								
8. Concomitant medication	X	X			X		X	X	X
9. Smoking	X								
10. Demographic data	X								
11. Inclusion/exclusion criteria	X								
12. CCS class	X						X	X	X
13. Working ability	X						X	X	X
14. QOL questionnaires	X						X	X	X
15. Clinical status	X						X	X	
16. ECG	X			X	X	X	X	X	
17. TTE	X				X		X	X	
18. 6-minute walk test	X						X	X	
19. PET/SPECT	X						X		
20. Review of coronary angio (< 6 months)	X								
21. Ophthalmologic examination *	X								
22. Thorax X-ray	X								
23. Laboratory tests	X	X		X	X	X	X	X	
24. PCR	X			X	X	X	X	X	
25. Hemodynamic evaluation	X			X	X		X	X	
26. Symptoms	X	X	X	X	X	X	X	X	X
27. Adverse events	X	X		X	X	X	X	X	X
28. Randomization			X						
29. Study drug preparation			X						
30. VEGF-$D^{\Delta NdC}$ gene/ placebo transfer			X						
31. NOGA mapping procedure			X						
32. Subject discharge					X				
33. Protocol deviations	X	X	X	X	X	X	X	X	X

BLOOD TESTS

A) Laboratory assessments prior to the study, at the screening visit:

- Blood count and platelets
- C-reactive protein
- Creatinine (P-Krea)
- Urea (P-urea)
- Creatinine-clearance (Pt-Krea-Cl)
- Alanine aminotransferase (P-ALT)
- Alkaline phosphatase (P-AFOS)
- Bilirubin (P-BIL)
- S-TG, S-chol tot., LDL, HDL, Lp(a), OxLDL
- Glucose (P-gluk, HbA1C)
- Sodium (P-Na)
- Potassium (P-K)
- Creatine kinase (CK)
- CK-MBm
- Troponin T (TnT)
- Prostate specific antigen (PSA) (men)
- Brain natriuretic peptide (proBNP)
- Total cholesterol, HDL, LDL, triglycerides, Lp(a), OxLDL
- HCG (for females in fertile age)
- Sediment and urine analysis
- VRAb-1
- Anti-VEGF-D antibody I
- VEGF-D ELISA sample
- Anti-adenovirus antibody I (AVAb I)
- Plasma sample, serum sample, white blood cell buffy coat and urine sample will be collected for future safety testing. Samples will be stored at -70°C for PCR analyses.

EXERCISE TEST
6-MINUTE WALKING TEST

To evaluate functional work capacity, a symptom limited 6-minute walking test will be performed at baseline, at 6 and 12 months.
(Primary endpoint after the 6 months follow-up).

The subject is asked to walk along a flat surface and to attempt to reach as far as possible. He/she may stop to rest and resume walking or choose to terminate the test when he/she can walk no further.

A modified Borg Scale used to assess perceived dyspnea and fatigue before and after the walk with a subjective numerical scale from 0 to 10.

Heart rate and oxygen saturation (using pulse oximetry) are measured before, during and after the test. ECG, blood pressure before, after and 3 min after the test.

The test score is reported and the **distance walked** rounded to the nearest meter. In addition, **heart rate and the distance at which angina pectoris or equivalent appeared will be recorded.**

This test is according to EMA guidelines and scientific advice from FIMEA.

EXERCISE TEST
6-MINUTE WALKING TEST

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NEWSFEED

May 8, 2017

Bittium Faros ECG devices' arrhythmia detection algorithms receive approval in Europe

OULU, FINLAND, 4 May 2017 - Bittium Faros ECG-measuring devices' built-in algorithms for detection of arrhythmias have received medical device approval in Europe. The algorithms can be used to automatically identify sequences from the heart measurement data that include atrial fibrillation, tachycardia, bradycardia, and pauses in the operation of the heart. Early detection of atrial fibrillation can be used to predict the risk of stroke and to prevent its emergence with timely treatment initiation. These new medical device approved algorithms for detection of arrhythmias are available now with Faros ECG-measuring devices.

THE MPW REVIEW

Take a look at the medicalphysicsweb reviews - all previous editions are available to view here.

KEY SUPPLIERS

RaySearch Laboratories

CIRS

TRANSHORACIC ECHO

When recruiting the patients for the trial transthoracic echocardiography (TTE) will be performed for the measurement of the wall thickness of the left ventricle.

Left ventricular function will be calculated by using **Teicholtz-method in M-mode and Simpson method** in 2-D images for the evaluation of global left ventricular function. Valvular functions and dysfunctions will also be measured.

After the gene transfer a repeated TTE will be done for the evaluation of possible **pericardial tamponation or other complications**. TTE will be repeated daily during the hospital stay.

TTE will be repeated for the measurement of global and regional left ventricular function at 6 and 12 months.

MYOCARDIAL PERFUSION

PET or SPECT

Any of the **PET tracers can be used (15O-H2O, 13N, 83Rb)** with appropriate tracer specific imaging protocol.

Typically, a dynamic PET scan of the heart is performed after injection of the tracer **at rest**. After decay of radioactivity, a second scan is performed **during adenosine-induced stress.**

The perfusion studies are analyzed using a validated software (Carimas version 2.92) blinded to the treatment, clinical data and time point [75] in a core laboratory (PET Centre, Turku University Hospital).

With **SPECT perfusion imaging either 99mTc-tetrofosmin or -sestamibi as a** tracer will be used. The standard guideline-based protocol is used.

For all imaging data, the LV is divided into standardized **17 segments model**. Regional myocardial blood flow (**MBF**) of the 17 segments is calculated both at rest and during stress. Myocardial perfusion reserve (**MPR**) is calculated for each segments as the ratio of MBF during adenosine stress and at rest.

MYOCARDIAL PERFUSION

PET or SPECT

To optimize the ideal target of gene therapy, the perfusion information is used to select the viable area where perfusion is compromised during stress.

To assess the changes in MBF and MPR after the therapy **two areas of interest** are defined. Region of

(1) the myocardial **area in which the therapy will be/was given** (usually the **area with low perfusion reserve**) and

(2) **reference** MPR as the myocardial segment with **the highest MPR** at baseline PET imaging.

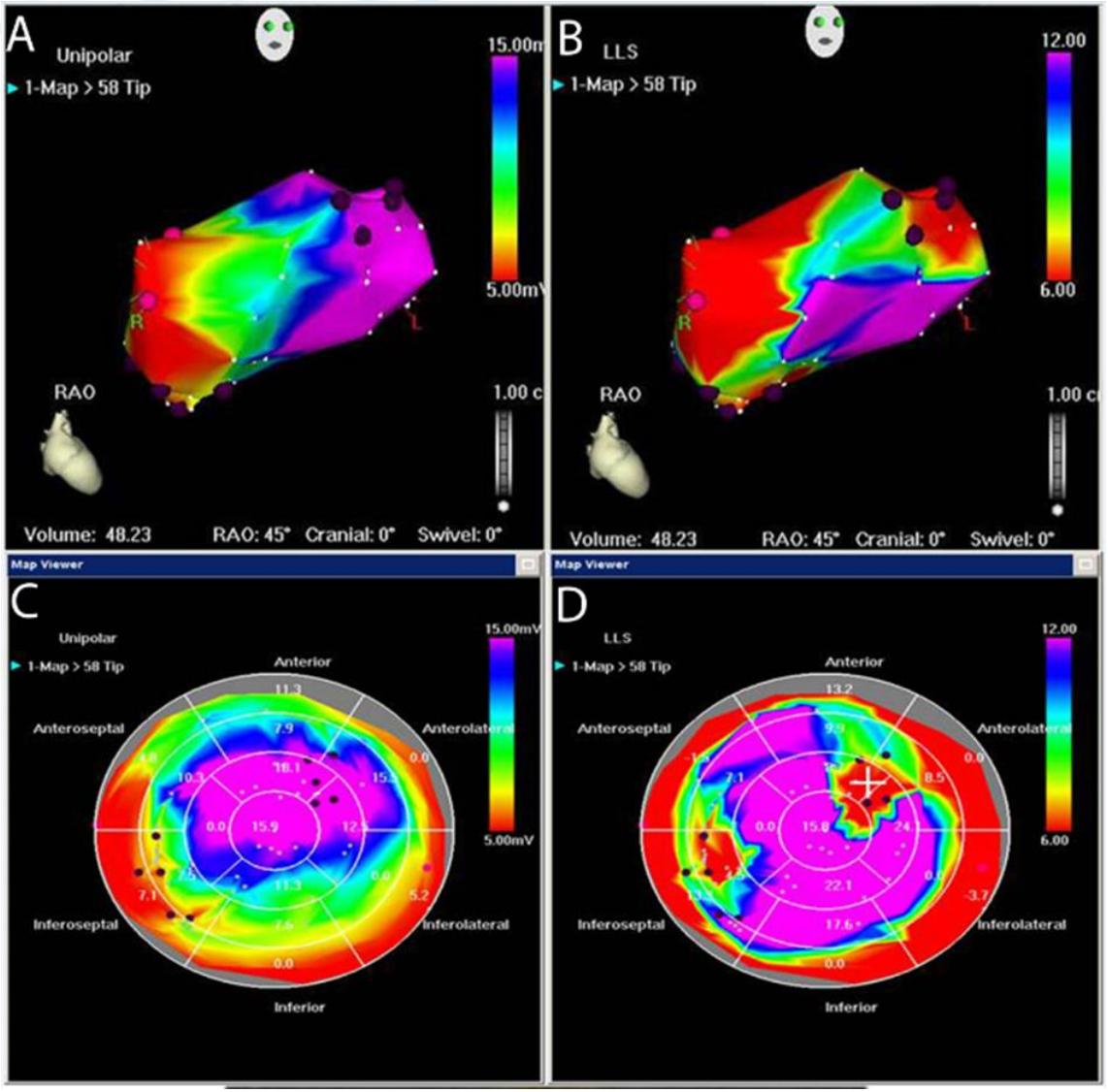
A significant novel improvement is the method developed in the phase I trial, where NOGA injection map is overlaid to the PET map to localize exactly the areas where AdVEGF-DdNdC will be injected.

For relative analysis the relative perfusion in the therapy area is correspondingly compared with the best perfused reference region.

The analysis is blinded for clinical findings and treatment groups. A core laboratory at Turku University Hospital, Turku, Finland (prof. Juhani Knuuti) will perform the image analysis centrally in a blinded manner.

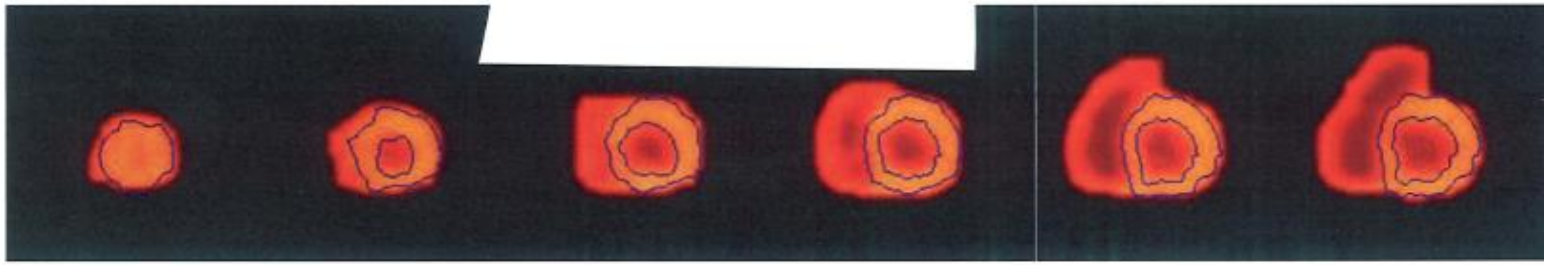
MYOCARDIAL PERFUSION

NOGA



MYOCARDIAL PERFUSION

PET - REST



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Patient ID:	
Patient gender:	---
Study description:	d5064,d5065
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Isotope:	15O
Radiopharmaceutical:	H2O – water
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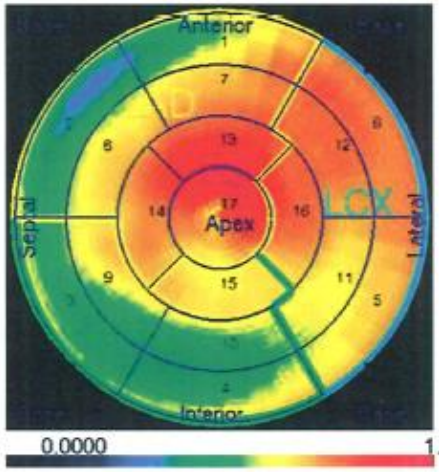
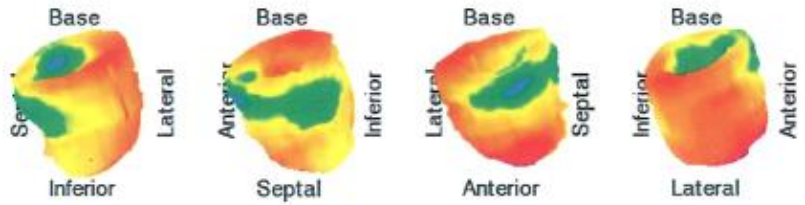
Input function:	Image_based
Modeling method	water
Frame limits	



	Flow ml/g/min	Va	PTF
GLOBAL	0.7782	0.7321	0.1676
LAD	0.8344	0.6736	0.1939
RCA	0.6450	0.8749	0.1521
LCX	0.8252	0.7320	0.1242
LADwa	0.7607	0.7370	0.2106
APEX	0.9519	0.6020	0.1728
Seg 1	0.6380	0.7984	0.1409
Seg 2	0.4125	0.8206	0.3430
Seg 3	0.5861	0.8641	0.2011
Seg 4	0.6400	0.8960	0.0755
Seg 5	0.7816	0.8040	0.1425
Seg 6	0.8582	0.6947	0.1316
Seg 7	0.7957	0.8085	0.1181
Seg 8	0.7555	0.8232	0.2560
Seg 9	0.6546	0.8800	0.2186
Seg 10	0.5690	0.9776	0.0911
Seg 11	0.7235	0.8001	0.1244
Seg 12	0.8966	0.7258	0.1086
Seg 13	1.0106	0.6440	0.1462
Seg 14	0.8874	0.6893	0.2360
Seg 15	0.7375	0.8099	0.1522
Seg 16	0.8787	0.6677	0.1178
Seg 17	0.9519	0.6020	0.1728



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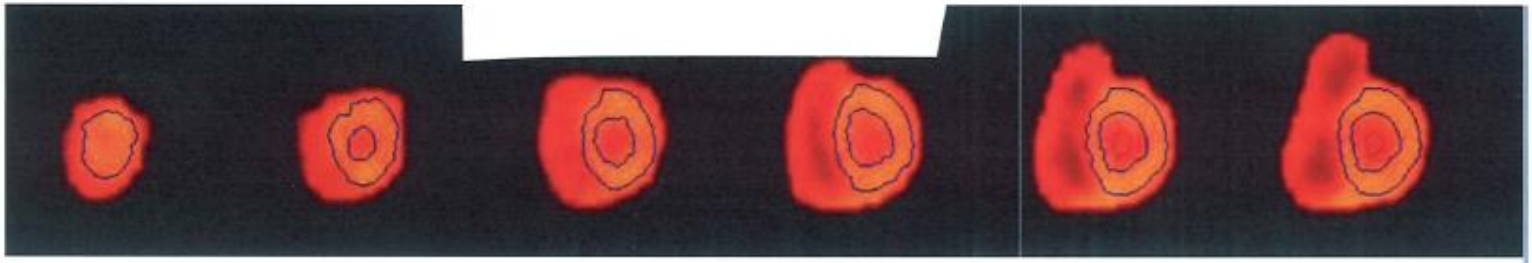
MYOCARDIAL PERFUSION

PET - EXERCISE



Patient name:
Patient ID:
Patient gender:
Study description: d5064,d5065
Institute: TURKU PET CENTRE
Isotope: 15O
Radiopharmaceutical: H2O – water
Data file: i831599.PTDC.1
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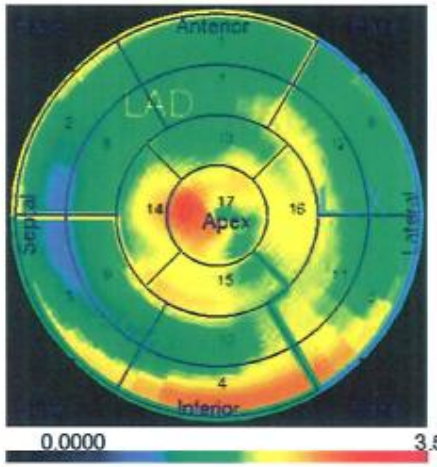
Modeling method water
Frame limits



	Flow ml/g/min	Va	PTF
GLOBAL	1.9956	0.6955	0.2491
LAD	2.0273	0.6871	0.2468
RCA	1.9290	0.7266	0.2858
LCX	1.9789	0.6850	0.2212
LADwa	1.7976	0.6982	0.2628
APEX	2.3668	0.6812	0.2225
Seg 1	1.7190	0.7604	0.1647
Seg 2	1.4930	0.5316	0.4518
Seg 3	1.6711	0.6499	0.3841
Seg 4	2.5833	0.8303	0.2033
Seg 5	1.9949	0.6861	0.2665
Seg 6	1.8226	0.6847	0.2059
Seg 7	1.8149	0.8488	0.0981
Seg 8	1.6209	0.7012	0.2772
Seg 9	1.5600	0.6632	0.3466
Seg 10	1.7641	0.7592	0.2645
Seg 11	2.0061	0.7011	0.1981
Seg 12	1.9065	0.6874	0.2224
Seg 13	1.8127	0.7455	0.1802
Seg 14	2.1439	0.6647	0.3371
Seg 15	2.0742	0.7596	0.2267
Seg 16	2.1111	0.6759	0.2127
Seg 17	2.3668	0.6812	0.2225

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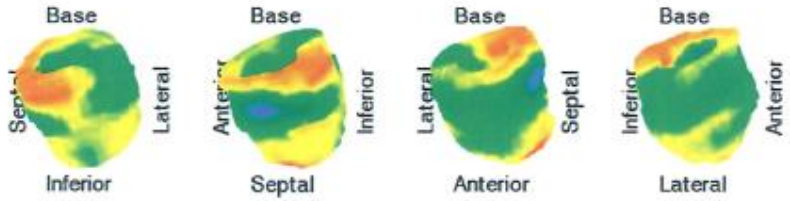
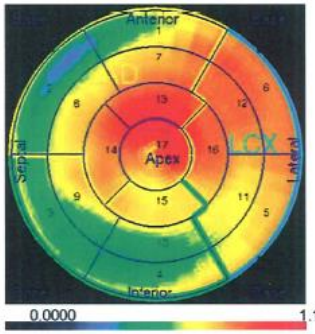
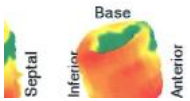


MYOCARDIAL PERFUSION

PET, NOGA, CORONAY ANGIOGRAPHY

PET REST





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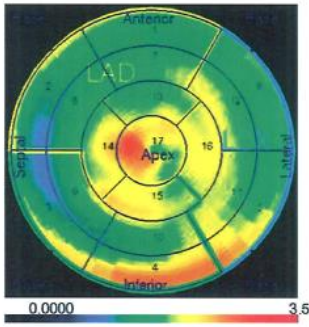
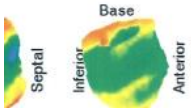
PET EXERCISE





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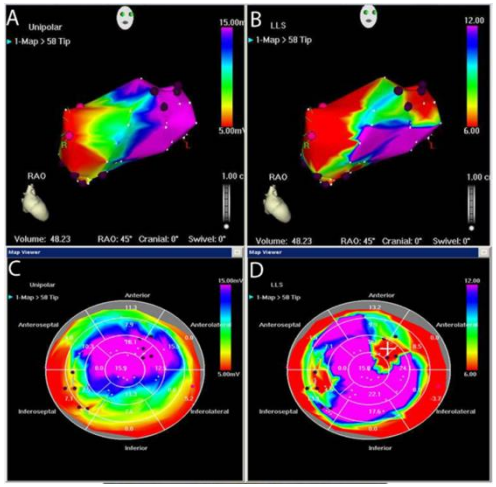
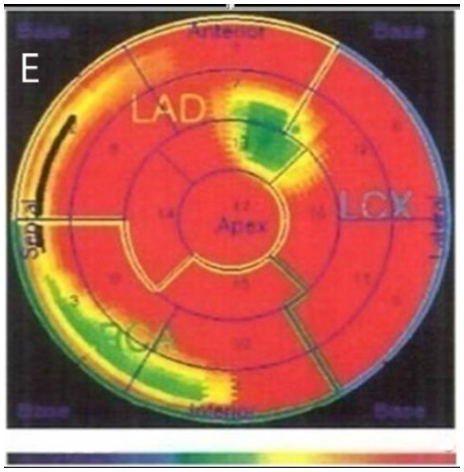
Seg 16	2.1111	0.6759	0.2127
Seg 17	2.3668	0.6812	0.2225

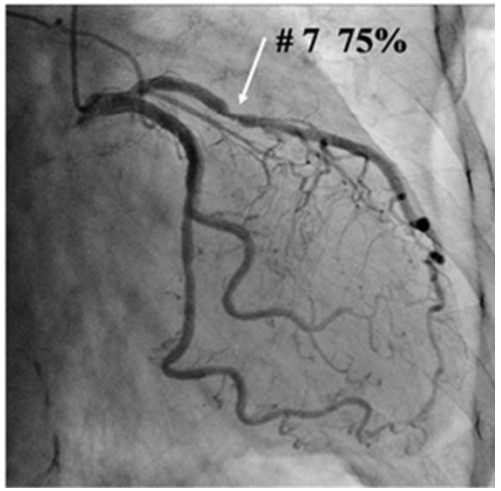
NOGA



PET MPR



ANGIO REST



LV MAPPING

Endocardial gene transfer will be under fluoroscopic guidance.

8.0 F introducer sheath will be inserted into the common femoral or superficial femoral artery and an electroanatomical mapping an injection catheter (NOGA©, Cordis Corp., Johnson & Johnson company, Miami Lakes, Florida) will be introduced into the left ventricle crossing the aortic valve (**transaortic approach**).

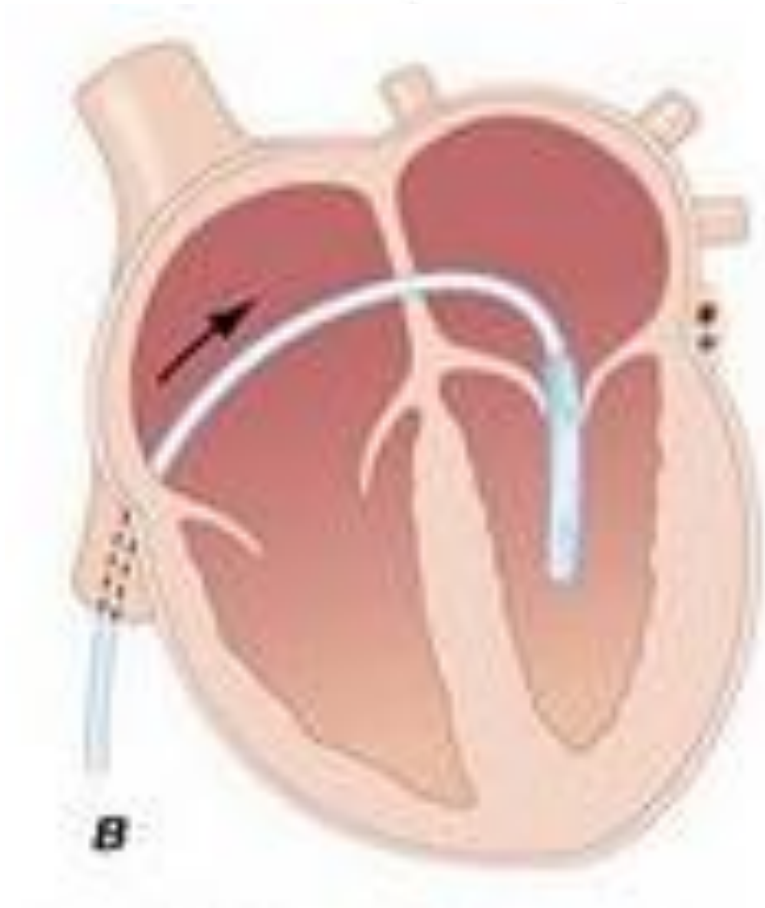
Alternatively, the 8.0 F introducer sheath is inserted in the femoral vein. A transseptal quiding catheter (Agilis) with a transseptal needle is used to perform transseptal puncture and finally the electroanatomical catheter will be introduced into the left ventricle (**transseptal approach**).

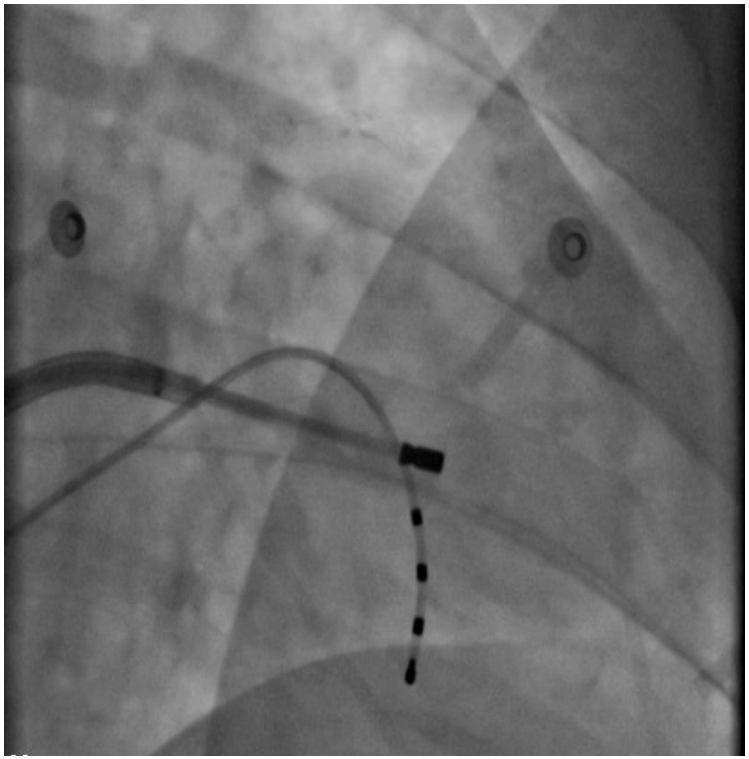
Heparin (unfractionated or fractionated) is given to maintain ACT > 300.

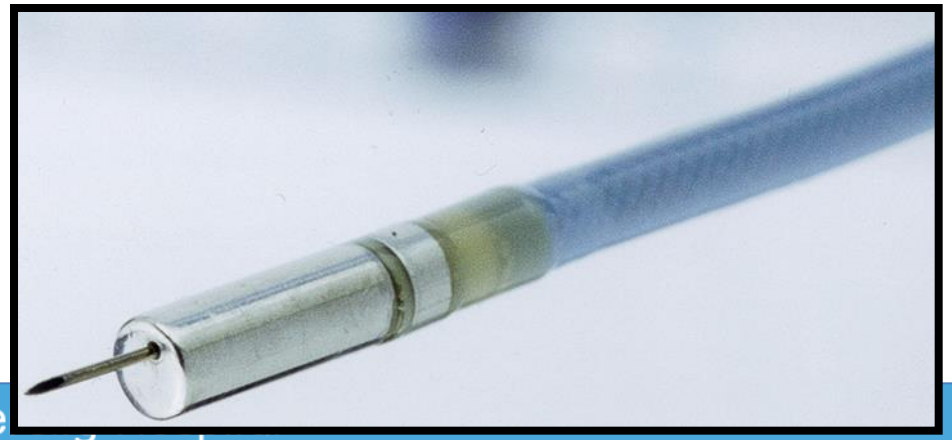
Left ventricular endocardium will be mapped spot-by-spot to evaluate the most **optimal sites for the gene injections in combination with the results of PET/SPECT and coronary angiography analysis**.

TRANSSEPTAL APPROACH

KAT-301







GENE INJECTION

After the electroanatomical mapping and definition of sites for gene transfer a dose of 1x1011 vpu of AdVEGF-DdNdC or matching placebo will be injected into 10 sites of the myocardium (0.2 ml per site).

The depth of the injection is approximately 5 mm and the injections will be localized 5 to 10 mm apart from each other.

INVESTIGATIONAL DRUG PRODUCT

First generation replication-deficient AdVEGF-D produced in 293 cells will be injected into ten sites in the endocardium.

The dose of 1x1011 vp in a total volume of 2 ml (10 times 0.2 ml) will be used.

Control patients will be treated and operated exactly in the same way except that placebo (buffer solution without gene) injection into the myocardium is used.

POSTPROCEDURE MONITORING

Patients are followed for the possible signs of adverse reactions.

After the procedure the patients will be transferred to a cardiac bed ward.

Hemodynamic parameters (ECG monitoring, heart rate, blood pressure) will be continuously recorded. **12-lead ECG, laboratory follow-up and repeated TTE** will be performed for the safety reasons on 1st postoperative day and repeated if necessary.

Patients are **discharged 1 day after** the procedure.

ADVERSE EVENTS

AE

All adverse events are classified as either serious or non-serious based on strictly objective definitions (see details in Appendix 2).

Adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease whether or not related to the investigational therapy

This includes events not seen on baseline or worsened even if present at baseline.

SERIOUS ADVERSE EVENTS

SAE

Serious adverse event (SAE) is defined as any untoward medical occurrence that:

- **results in death**
- **is life-threatening**
- **requires in-subject hospitalization or prolongation of existing hospitalization**
- **results in persistent or significant disability/incapacity**
- **is a congenital anomaly or birth defect**

Generally, in-subject hospitalization must include an overnight admission.

Pre-planned elective procedures are not to be reported as serious adverse events.

In the life-threatening event the subject is at risk of death at the time of the event.

SEVERITY OF EVENTS

AE and SAE

Severity assessment of (S)AE:

- **Mild:** Transient symptoms, no interference with patient's daily activities, acceptable
- **Moderate:** Marked symptoms, moderate interference with patient's daily activities, but still acceptable
- **Severe:** Considerable interference with patient's daily activities, unacceptable

CAUSALITY OF EVENTS

AE and SAE

- **Not related: An adverse event, which is not related to the investigational therapy**

- **Unlikely: An adverse event for which an alternative explanation is more likely with concomitant medication or illness**

- **Possibly: An adverse event, which might be due to the use of the investigational therapy. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.**

- **Probably: An adverse event, which might be due to the use of the therapy. The relationship in time is suggestive.**

- **Definitely: An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by alternative explanation. The relationship in time is very suggestive.**

REPORTING OF ADVERSE EVENTS

AE

All adverse events and serious adverse events will be recorded and reported to Kuopio University Hospital and

further to Finnish Medical Agency (FIMEA), Ethics Committee, Data & Safety Monitoring Committee and competent authorities in each participating country.

eCRF

The study data is stored using a web-based electronic Case Report Form (eCRF) tool.

The study patients will be identified only with Subject identification number, initials, and study ID number.

The original patient records will be archived in the study centers.

The methods used to collect, check, validate and process study data are described in detail in the Data Management Plan and Data Validation Plan.

CRF - PRINTED

CASE REPORT FORMS

Study Code: ReGenHeart

Clinical development and proof of principle testing of new regenerative VEGF-D therapy for cost-effective treatment of refractory angina

A phase II randomized, double-blinded, placebo-controlled study

Center number	☐☐☐☐
Screening number	☐☐☐☐
Randomization number	☐☐☐☐
Patient initials	☐☐☐☐

CRF - PRINTED

Study Code:ReGenHeart CRFs –Version 1.3 – 08-04-2016

Screening number: S 9	Subject initials: First Last	SCREENING VISIT

CLINICAL EXAMINATION

Body system	Normal	Abnormal, specify:	Not done
1. General appearance	☐	☐	☐
2. Head, eyes, ears, nose, throat	☐	☐	☐
3. Cardiovascular	☐	☐	☐
4. Respiratory	☐	☐	☐
5. Gastrointestinal	☐	☐	☐
6. Extremities	☐	☐	☐
7. Peripheral vascular	☐	☐	☐
8. Musculoskeletal	☐	☐	☐
9. Skin	☐	☐	☐
10. Neurologic	☐	☐	☐
11. Lymphnodes	☐	☐	☐
12. Urogenital	☐	☐	☐

MONITORING

The study will be monitored by a CRO company by means of regular on-site visits and checking of the CRFs with sufficient frequency to verify compliance with the protocol and applicable regulatory requirements and the completeness and accuracy of data. This will be done by verifying CRFs against original source documents.

Study monitors must have direct access to source documents, which support data on the CRF, e.g. hospital records and original laboratory records and subject informed consent forms.

Prior to the monitoring visits the investigator must ensure that source data has been signed and dated by the investigator, CRFs have been filled in and subject's source data is available for monitoring.

The monitoring of this study will be performed in accordance with the principles of ICH GCP Guideline. All relevant patient records must be available for the monitoring visits.