COVER PAGE

Clinical Protocol and Statistical Analysis

NCT Number: NCT01422772

Official Title:

Open-label, non-comparative, dose-escalation, single-center, phase 1 trial to evaluate the safety of VM202RY gene medicine injected into the cardiac muscle of incompletely revascularized area after CABG in patients with ischemic heart diseases.

Unique Protocol ID: **VM202RY-VM01**

Date of Protocol: **Jan 1, 2007**

CONFIDENTIAL

CONFIDENTIAL

Synopsis

Title	Open-label, non-comparative, dose-escalation, single-center, phase 1 trial to evaluate the safety of VM202RY gene medicine injected into the cardiac muscle of incompletely revascularized area after CABG in patients with ischemic heart diseases
Investigational product	Lyophilized plasmid DNA, pCK-HGFX7 (2mg/vial) containing 44mg sucrose and 36mg NaCl
Sponsor	ViroMed Co., Ltd.
Clinical site & Principal investigator	• Clinical site: Seoul National University Hospital • Principal investigator: Ki-bong Kim
Clinical protocol No.	VM202RY-VM01
Clinical design	Open-label, non-comparative, dose-escalating, single-center
Clinical phase	Phase I
Purpose of clinical trial	Safety evaluation of direct myocardial injection of VM202RY into coronary artery areas where complete revascularization by coronary artery bypass grafting is not achieved
Subject	All patients who are candidates for coronary artery bypass grafting are included, and patients in the surgical target area with decreased myocardial perfusion are expected to have incomplete revascularization in some myocardial areas due to poor vascular condition (e.g., calcified vessels, diffuse atherosclerotic vascular disease, small vessels with a diameter of less than 1 mm) that make it impossible to perform vascular anastomosis during surgery.
Inclusion and Exclusion criteria	**Inclusion criteria** 1) Patients aged between 19 and 75 years (inclusive). 2) Patients whose myocardial SPECT scan of the coronary artery region shows a decrease in perfusion of 7% or more in the stress image compared to the resting image. 3) Patients for whom coronary angiography shows either a coronary artery diameter of 1 mm or less, diffuse atherosclerosis, or severe calcification, and who are thus considered to have a potential for incomplete revascularization during surgery, or for whom coronary artery bypass surgery is judged to be infeasible in some myocardial perfusion areas. 4) Patients who, prior to the start of the clinical trial, have provided written informed consent either themselves or through a legal representative, and who are able to comply with the requirements of the clinical trial. **Exclusion criteria** 1) Patients with ongoing heart failure or symptomatic heart failure (Killip class II or higher or left ventricular ejection fraction < 25% on echocardiography). 2) Patients with uncontrolled ventricular arrhythmia on ECG or a history of treatment for ventricular arrhythmia.

	3) Patients with current or a history of malignant tumors. 4) Patients with current serious infectious diseases. 5) Patients with uncorrected hematologic disorders. 6) Patients requiring concomitant valvular surgery or left ventricular volume reduction surgery. 7) Patients with current or a history of proliferative retinopathy. 8) Patients with severe comorbidities expected to cause death within 1 year (i.e., during the clinical follow-up period). 9) Patients with a history of drug or alcohol abuse within the past 3 months. 10) Pregnant or breastfeeding women, and women of childbearing potential who have not reached menopause. However, women who have undergone surgical sterilization procedures such as hysterectomy or bilateral tubal ligation may participate in the trial. Even if a woman agrees to use contraception, she may not be enrolled in the trial unless surgically sterilized. 11) Patients deemed inappropriate for clinical trial participation by the investigator. 12) Patients with cerebrovascular disease (e.g., current or within the past 6 months: cerebral infarction, cerebral hemorrhage, or transient ischemic attack). 13) Patients diagnosed with essential hypertension according to JNC VII whose blood pressure is not controlled with medication. 14) Patients with severe hepatic impairment (including those with AST or ALT levels ≥ 2 times the upper limit of normal [currently 40 IU/L] before administration of the investigational drug). 15) Patients with severe renal impairment (including those with serum creatinine > 2 mg/dL, anuria, acute renal failure, or those undergoing dialysis before administration of the investigational drug). 16) Patients who have undergone coronary artery bypass graft (CABG) surgery. 17) Patients who have undergone vascular angioplasty within 1 year prior to enrollment in this clinical trial.
Target enrollment number of subjects	3 subjects per group completed all clinical trials, totaling 9 subjects • Up to 18 people can be registered when DLT occurs • However, if no DLT occurs after registering 3 subjects per test group, the dose is sequentially increased to register 9 subjects. • If there are dropouts during the follow-up period (24 weeks), additional recruitment will be conducted so that the final number of completed subjects will be 3 per group, totaling 9.
Schedule of clinical trial	Approximately 38 months from the date of approval of the clinical trial plan by the Commissioner of the Ministry of Food and Drug Safety • Screening period: 3 weeks • Treatment: 7 days • Follow-up: 24 weeks • Patient recruitment period of approximately 128 weeks

	and patient follow-up observation period of approximately 152 weeks
Name of investigational product	VM202RY
Dosage and administration	**Administration** After CABG procedure, dissolve 2mg (1vial) of VM202RY in 4mL of sterile distilled water, leave at room temperature for 5 minutes to completely dissolve, then put it in a 1mL sterile syringe (27G) and immediately inject into the muscle. **Dosage** 1) Cohort 1: In the area where incomplete revascularization occurred after coronary artery bypass grafting, 0.5 mg/1 mL of VM202RY was administered intramuscularly to 4 sites (0.125 mg/0.25 mL/injection point). 2) Cohort 2: VM202RY 1mg/2mL was administered intramuscularly to 8 sites (0.125mg/0.25mL/injection point) in areas with incomplete revascularization after coronary artery bypass grafting. 3) Cohort 3: In the area where incomplete revascularization occurred after coronary artery bypass grafting, VM202RY 2mg/4mL was divided into 8 points (0.25mg/0.5mL/injection point) and administered intramuscularly.
Examination	1. Blood test 2. Blood chemistry 3. Serum test 4. Blood clotting test 5. Urine test 6. Urine pregnancy test (for women only) 7. ECG 8. Cardiac enzyme 9. Chest X-ray examination 10. Echocardiography 11. Myocardial SPECT 12. Cardiac MRI 13. Coronary angiography 14. Fundoscopy 15. anti-HGF antibody 16. HGF protein in serum 17. Tumor marker test/fecal occult blood test
Endpoints	**Primary endpoint:** - **Safety: evaluated for 6 months after VM202RY administration** 1) Dose Limiting Toxicity (DLT) 2) Tolerated Dose (TD) 3) Adverse reactions, vital signs, physical examination and laboratory test results 4) Major adverse cardiovascular events (MACE): Hospitalization for cardiac death, myocardial infarction, ventricular arrhythmia requiring treatment, or target vessel

	revascularization 5) Safety evaluation of intramuscular injection of VM202RY: Evaluation for persistent bleeding, arrhythmia, and other complications **<u>Secondary endpoint:</u>** - **Efficacy** 1) Cardiac function: Left ventricular ejection fraction and regional cardiac function by cardiac MRI, myocardial SPECT, and echocardiography 2) Viable myocardium: Cardiac MRI (myocardial thickness of the intramuscular injection area, extent of gadolinium late enhancement, and exercise intensity of the region) 3) Changes in myocardial ischemic area: Myocardial SPECT (blood flow changes in the intramuscular injection area at rest and under load) - **HGF concentration in blood** 1) Changes in plasma HGF concentration after VM202RY administration - **Anti-HGF antibody production by VM202RY administration** 1) Comparison of ELISA results using serum from subjects administered with VM202RY
Statistics	**<u>Primary endpoint</u>** - **Safety evaluation** 1) Dose limiting toxicity Dose-limiting toxicity is assessed 4 weeks after administration of the investigational product, VM202RY and refers to cases where toxicity of Grade 3 or higher occurs based on the WHO Toxicity scale or severe adverse reactions occur according to the Spilker classification system. However, adverse reactions accompanying coronary artery bypass grafting (CABG) are excluded. 2) Tolerated dose The subjects are registered sequentially from Step 1 as follows to confirm the tolerance capacity. 1. After enrolling 3 subjects in the first dose group and evaluating DLT 4 weeks after administration to the third subject, 1-1. No DLT occurred in any of the 3 patients (0/3) → 3 patients enrolled in the second dose group (A) 1-2. DLT occurred in 1 out of 3 patients (1/3) → Additional registration of 3 patients with the same dose 1-2-1. No DLT occurrence for all 3 added (1/6) → 3 people registered in the second dose group (A) 1-2-2. 1 out of 3 additional patients developed DLT (2/6) → Stop increasing dose

1-3. DLT occurred in 2 out of 3 patients (2/3) → Dose escalation stopped

2. Enroll 3 subjects in the second dose group, administer the third subject, and evaluate DLT 4 weeks later
2-1. No DLT occurred in any of the 3 patients (0/3) → 3 patients enrolled in the third dose group (B)
2-2. DLT occurred in 1 out of 3 patients (1/3) → Additional registration of 3 patients with the same dose
2-2-1. No DLT occurrence for all 3 added (1/6) → 3 people registered in the third dose group (B)
2-2-2. DLT occurred in 1 out of 3 patients added (2/6) → Stop increasing dose (A)
2-3. DLT occurred in 2 out of 3 patients (2/3) → Stop dose increase (A)

3. The third dose group: enroll 3 subjects and DLT evaluation is conducted 4 weeks later after administration of the third subject.
3-1. No DLT occurres in any of the 3 patients (0/3) → Clinical trial ends (C)
3-2. DLT occurred in 1 out of 3 patients (1/3) → Additional registration of 3 patients with the same dose
3-2-1. No DLT occurres in any of the 3 additional patients (1/6) → Clinical trial ends (C)
3-2-2. DLT occurres in 1 out of 3 patients added (2/6) → Clinical trial ends (B)
3-3. DLT occurres in 2 out of 3 patients (2/3) → Clinical trial ends (B)

Tolerated dose

Condition	Tolerated dose
A + B + C	C
A + B	B
A	A

3) Adverse reactions, vital signs, physical examination and laboratory test results
All adverse reactions and their severity are presented by dose group, and the incidence rate and 95% confidence interval are estimated. If comparison is possible, Fisher's Exact Test is used to test.
Vital signs (blood pressure, body temperature, pulse, respiration) are presented in descriptive statistics by group and visit to examine trends in change.
The physical examination presents, by group, the items of physical examination that showed abnormalities before and after administration.
Among laboratory tests, general blood tests and general

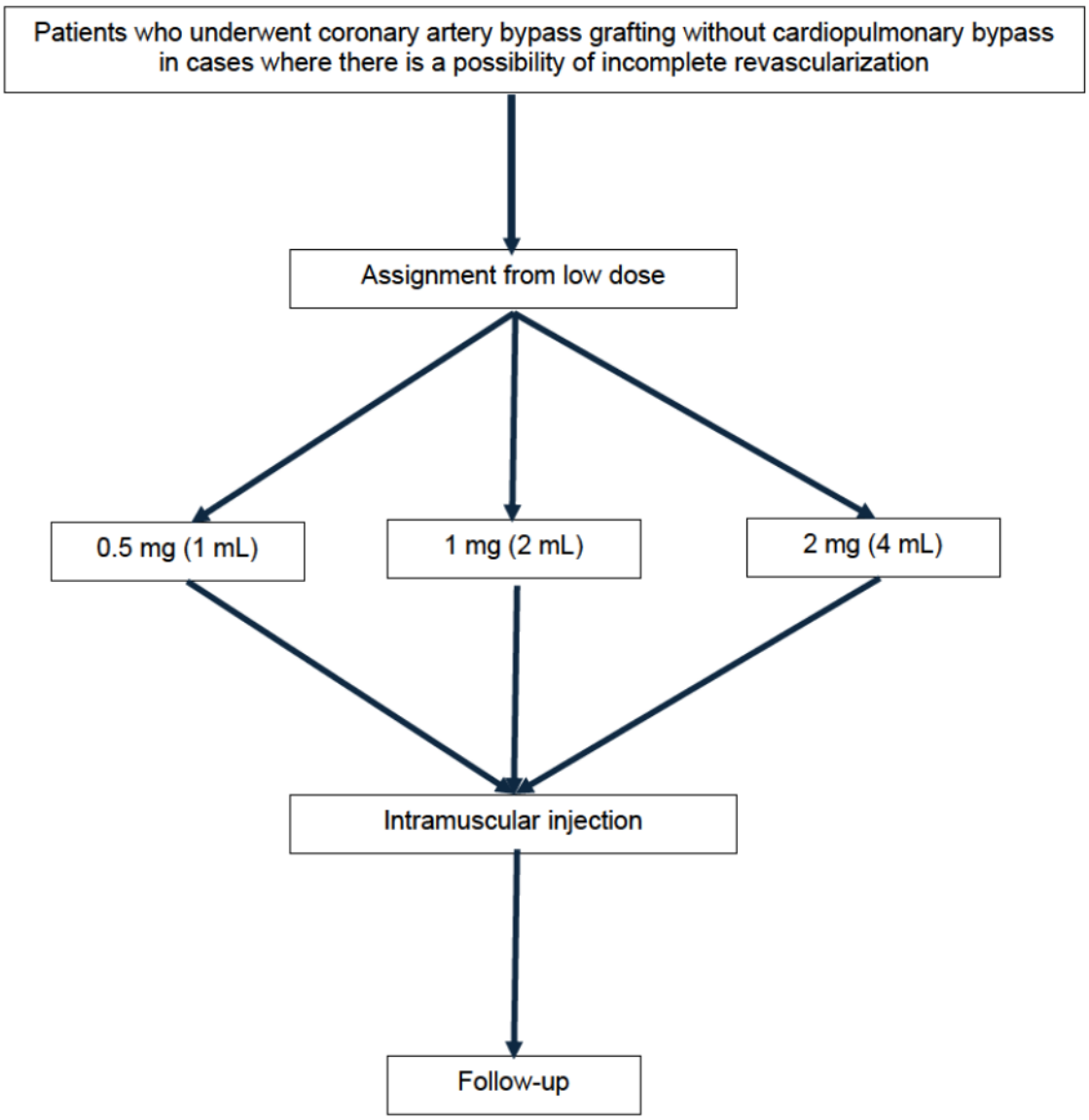
	chemistry tests are presented with descriptive statistics by group and visit to examine the trend of change. In the case of urine tests, the frequency and ratio of changes from normal before administration to abnormal after administration are presented by group and visit to examine the trend of change. 4) Major adverse cardiac event (MACE) MACE is defined as “cardiac death, myocardial infarction, ventricular arrhythmia requiring treatment, or hospitalization for target vessel revascularization” and comparisons between treatment groups are tested using Fisher’s Exact Test. 5) Safety evaluation of intramuscular injection of VM202RY The frequency of persistent bleeding, arrhythmia, and other complications occurring after VM202 administration is presented by administration group, and comparisons between groups are tested using Fisher's Exact Test. **<u>Secondary endpoint</u>** - **Efficacy evaluation** 1) Cardiac function The evaluation of cardiac function (left ventricular ejection fraction by cardiac MRI, myocardial SPECT, and echocardiography) was tested using the Kruskal-Wallis test for group differences in changes before and after VM202RY administration. 2) Viable myocardium The evaluation of the size of the viable myocardium (cardiac MRI: myocardial thickness in the VM202RY injection area, extent of gadolinium late enhancement, and exercise intensity in the regional region) was tested using the Kruskal-Wallis test for group differences in changes before and after VM202RY administration. 3) Myocardial ischemic area Evaluation of myocardial SPECT (blood flow changes in the injection area at rest and under load) is tested using the Kruskal-Wallis test for group differences in changes before and after VM202RY administration. - **HGF concentration in blood** Measure and observe plasma HGF concentrations and examine whether there is a correlation between the results and the degree and pattern of adverse reactions. - **Anti-HGF antibody production by VM202RY administration** Correlation between anti-HGF antibody production and cardiac function improvement is evaluated.

Schedule of evaluations and visits

Procedure	Screening	Treatment					Follow-up				
Visit schedule	-21 ~ -1 day	Day 0	Day 1	Day 2	Day 5	Day 7	Week 2 (±4D)	Week 4 (±4D)	Week 8 (±7D)	Week 12 (±7D)	Week 24 (±7D)
Informed consent	X										
Inclusion / Exclusion criteria	X	X									
CABG+intramyocardial injection		X									
Physical exam	X	X					X	X	X	X	X
Clinical symptoms and adverse reactions		X	X	X	X	X	X	X	X	X	X
Basic information on subject	X										
Medical history	X										
Hematology	X	X	X	X	X	X	X	X		X	X
Biochemistry	X		X	X	X	X	X	X		X	X
Urinalysis	X		X	X	X	X	X	X		X	X
Urine pregnancy test	X										
ESR / CRP	X		X			X	X	X		X	X
CK, CK-MB, LDH, Troponin I	X	X	X	X	X	X	X	X		X	X
Serology	X										
PT, aPTT, Fibrinogen	X										
Anti-HGF antibody	X						X	X			X
Serum HGF protein	X					X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X	X	X	X	X	X	X	X		X	X
Holter monitoring	X					X	X	X		X	X
Cancer marker test / fecal occult blood test	X									X	X
Fundoscopy	X						X	X		X	X
MIBI SPECT	X									X	X
MRI	X									X	X
TTE	X					X				X	X
CAG	X										X
Concurrent medication	X	X	X	X	X	X	X	X	X	X	X

* Day 0: testing and blood sampling on day 0 of surgery are performed prior to surgery. If the screening test results are available within 24 hours of surgery, the day 0 test may be omitted and replaced with the screening results.
- Treatment (7 days): subjects are hospitalized and treated.
- Long-term follow-up observations are conducted 1, 2, 3, 4, and 5 years after VM202RY administration to confirm the subject's survival and occurrence of cancer.

Procedure


Patients who underwent coronary artery bypass grafting without cardiopulmonary bypass in cases where there is a possibility of incomplete revascularization
Assignment from low dose
0.5 mg (1 mL)
1 mg (2 mL)
2 mg (4 mL)
Intramuscular injection
Follow-up

Abbreviations

ADR: Adverse Drug Reaction

AE: Adverse Event, Adverse Experience

aPTT: active Partial Thromboplastin Time

CABG: Coronary Artery Bypass Graft

CAG: Coronary Angiography

CEA: Carcino Embryonic Antigen

CK: Creatine Kinase

CK-MB: Creatine Kinase MB fraction

CRA: Clinical Research Associate

CRF: Case Report Form

CRO: Contract Research Organization

CRP: C-Reaction Protein

ECG: Electrocardiogram

ESR: Erythrocyte Sedimentation rate

HGF: Human hepatocyte growth factor

ITT: Intent-to-Treat

JNC VII: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII

KGCP: Korean Good Clinical Practice

MACE: Major Adverse Cardiac Event

MIBI SPECT: 99mTc Sestamibi Methoxyl Isobutyl Isonitrile Single Photon Emission Computed Tomography

MRI: Magnetic Resonance Imaging

pCK-HGFX7 (VM202RY): A plasmid DNA-based therapeutic product expressing human hepatocyte growth factor (HGF) for angiogenic therapy in patients with cardiovascular disease

POD: Postoperative Day

PP: Per-Protocol

PSA: Prostate Specific Antigen

PT: Thrombin Time

Q-PCR: Quantitative polymerase chain reaction assay

SAE: Serious Adverse Event, Serious Adverse Experience

TTE: Trans Thoracic Echocardiography

VEGF: Vascular endothelial growth factor is an angiogenic cytokine

VSMC: Vascular smooth muscle cells

CONTENTS

1. Title of clinical trial

Open-label, non-comparative, dose-escalation, single-center, phase 1 trial to evaluate the safety of VM202RY gene medicine injected into the cardiac muscle of incompletely revascularized area after CABG in patients with ischemic heart diseases

2. Clinical site

- Site name: Seoul National University Hospital
- Address: 28 Yeon-gun dong, Jong-no gu, Seoul, 110-799

3. Principal investigator and staff

3.1 Principal investigator

Name	Affiliation	Title
Ki-bong Kim	Department of thoracic and cardiovascular surgery, Seoul National University College of Medicine	Professor

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

-

4. Pharmacist

Name	Affiliation	Title
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5. Sponsor

- Name: ViroMed Co., Ltd
- CEO: [redacted]

5.1 Contact persons of Sponsor

- Sponsor: ViroMed Co., Ltd
- [redacted]

6. Contract research organization and clinical research agent

6.1 Contract research organization

- Name: CMIC Korea
- [redacted]

6.2 Clinical research agent

- CRO: [redacted]

7. Background

7.1 Gene therapies for ischemic heart disease

Ischemic heart disease has been the cause of death for more than six million people annually worldwide in recent years, and it is predicted to become the most common cause of

death in humans in the future [1]. Despite remarkable advances in coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for revascularization in the treatment of ischemic heart disease, approximately 10% of all coronary artery disease patients are reported to be unsuitable for revascularization [2]. Furthermore, even among patients undergoing CABG, about 20–25% experience incomplete revascularization, a figure that has remained largely unchanged in recent years [3]. The negative impact of such incomplete revascularization on patient survival has been demonstrated in multiple studies. While the effect of incomplete revascularization on survival in patients aged 75–80 years and older has shown mixed results—with some studies reporting reduced survival [4,5] and others reporting no difference [6]—in patients younger than 75, most studies have identified incomplete revascularization as an independent factor that reduces both short- and mid-term survival rates [7–9].

Although myocardial ischemia itself can induce angiogenesis and the formation of collateral vessels, this process is often insufficient to meet the myocardial demand for blood flow. Therefore, in patients for whom revascularization is either impossible or incomplete, the introduction of therapeutic angiogenesis using growth factors may offer a potential treatment to achieve complete revascularization and improve survival rates. Given the current lack of treatment options for incomplete revascularization, gene therapy for neovascularization, which could achieve complete revascularization, is considered a promising alternative. It likely meets the criteria outlined in Article 2 (in cases where no other treatments are available, or when gene therapy is expected to be significantly more effective than existing options) and Article 3 (when the Minister of Health and Welfare deems it necessary for disease prevention or treatment following review by an ethics committee) of the Bioethics and Safety Act concerning gene therapy.

Such gene therapy can involve directly injecting growth factor proteins or genes encoding growth factors, using various delivery systems, into the coronary arteries or myocardium. Among the most studied substances is vascular endothelial growth factor (VEGF), but studies reporting its effects on improving myocardial perfusion [10–17] have shown inconsistent results. Moreover, no studies have confirmed its contribution to improved cardiac function, casting doubt on its role in the treatment of ischemic heart disease.

Hepatocyte growth factor (HGF), originally discovered and cloned as a potent mitogen for hepatocytes [18,19], acts on the tyrosine kinase receptor c-Met found on cell membranes and has been reported to strongly induce proliferation, migration, angiogenesis, and inhibition of apoptosis in various cells [20,21]. Therapeutic angiogenesis using HGF has been shown to facilitate the formation of more ideal blood vessels in ischemic regions by promoting both endothelial cell proliferation and smooth muscle cell migration. It also inhibits apoptosis in the infarct border zone during the remodeling process after myocardial infarction, thereby contributing to improved myocardial function [22–24]. Additionally, the HGF-c-Met system present in the heart is known not only to support vascular formation but also to protect cardiomyocytes themselves, highlighting a new potential role for HGF in preventing heart failure after myocardial infarction [25–27].

7.2 Clinical trials using hepatocyte growth factor gene

As of 2006, the clinical trial status of HGF gene therapy is as follows: A phase III clinical trial is underway in Japan for ischemic limb disease, and a phase II trial is being conducted in the United States. For ischemic heart disease, a phase I/II trial is ongoing in the United States.

The following clinical trial results were reported by Morishita's group (Anges MG, Japan) in the June 2004 issue of Hypertension. These are results from a phase I/IIa clinical trial using the HGF gene for patients with ischemic limb disease [28].

The aim of this clinical trial was to assess the safety and efficacy of HGF gene therapy. Patients were recruited under the following conditions: chronic lower limb ischemia lasting more than 4 weeks accompanied by resting pain and untreatable ischemic ulcers; patients who continued drug therapy for at least 4 weeks after their hospital visit; patients who had not undergone percutaneous transluminal angioplasty; those without a history of cancer; patients without severe proliferative retinopathy; and patients with diabetes but without retinopathy. Among these, patients with an ankle-brachial index (ABI) below 0.6, measured twice weekly, and who showed no improvement after over 4 weeks of drug therapy were selected for the clinical trial.

A total of six patients participated in the trial—five males and one female. Among them, three patients had atherosclerotic vascular occlusion (two with diabetes, all three male) and three patients had Buerger's disease (two males and one female). The average age of the patients was 57.8 ± 4.5 years.

The HGF gene was loaded onto the pVAX1 plasmid vector (3.0 kb, Invitrogen Corporation) and administered to the patients. Gene administration was performed as follows: After a 4-week observation period post-admission, patients were first given a 0.4 mg dose of HGF gene to check for allergic reactions or anaphylaxis over a 2-week period. If no adverse effects were observed, a first full dose was administered two weeks later. The therapeutic dose was 2 mg/12 ml, administered twice at 4-week intervals. The injection sites were four areas of vascular occlusion determined via angiography. The study was completed 8 weeks after the second injection.

Efficacy and safety of the trial were evaluated based on the following indicators: ulcer size reduction, ELISA analysis of blood samples to detect acute or subacute allergies, anaphylaxis, or antibody formation, as well as measurements of pain (VAS - visual analog scale), quality of life (SF-36), transcutaneous oxygen tension (TcPO2), ABI, toe pressure index (TPI), digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and CT angiography.

Efficacy evaluation of HGF gene therapy was conducted as follows: Parameters were measured weekly for the first 12 weeks, then biweekly for the next 8 weeks, monthly for the next 12 weeks, and every 3 months for 2 years. The gene therapy was administered in conjunction with conventional treatments, including antibiotics, anticoagulants, and standard care for ischemic ulcers and necrotic tissue.

As a result of this clinical trial, no allergic, anaphylactic, or antibody responses were observed following HGF gene administration, thus demonstrating safety. Furthermore, the ABI increased by an average of 47.4% ($p<0.05$), pain decreased by an average of 40.7% ($p<0.05$), and a significant increase in TcPO2 ($p<0.05$) was also observed. The ulcer size decreased by an average of 44%, showing a statistically significant reduction ($p<0.05$). These findings suggest that HGF gene therapy is both safe and effective.

7.3 Overview and features of VM202RY

7.3.1 Features

(A) Delivery vector, pCK

The pCK gene delivery vector, which is currently used to carry the new hepatocyte growth factor (HGF), was used as the gene delivery vehicle for VMDA3601, the first gene therapy product in Korea to receive both product approval (February 20, 2001) and clinical trial approval (Phase I: May 2001; Phase II: December 2003) from the Korea Food and Drug Administration (KFDA). This gene therapy product carried vascular endothelial growth factor 165 (VEGF165) and was developed in collaboration with Dong-A Pharmaceutical and Samsung Medical Center, completing Phase I clinical trials in July 2003.

Furthermore, the pCK vector has been used to deliver various other genes in in vitro studies as well as in vivo experiments for the evaluation of therapeutic effects on viral myocarditis and arthritis, where its efficacy has been demonstrated. These results have been published in numerous scientific papers, proving its outstanding performance as a gene delivery vector.

Compared to conventional naked DNA vectors, the pCK gene delivery vector has the following characteristics:

1. Superior Gene Expression Efficiency: The pCK vector includes not only the promoter of the HCMV MIE (Human Cytomegalovirus Major Immediate-Early) gene, but also the non-coding sequence consisting of Exon 1, Intron A, and Exon 2 up to just before the translation initiation codon. This structure leads to more than 30-fold higher gene expression efficiency in both in vitro and in vivo settings compared to conventional vectors that use only the promoter.
2. Improved Safety Profile: Instead of the commonly used ampicillin resistance gene, the pCK vector incorporates a kanamycin resistance gene, thereby eliminating the risk of patient shock due to residual ampicillin after purification.
3. Optimized Vector Size for Mass Production: The pCK vector removes all unnecessary base sequences found in conventional gene delivery systems, thus minimizing vector size and offering the advantage of increased production yield during large-scale manufacturing.

[redacted]

[redacted]

7.3.2 Structural features

In the human genome, the HGF gene consists of 18 exons and 17 introns, and two isoforms are expressed through alternative splicing between exon 4 and exon 5. (A)

HGF-X genes are genomic-cDNA hybrid genes in which intron 4 sequences of various lengths are inserted between exon 4 and exon 5 of the HGF cDNA. (B)

HGF-X7 is the most optimized gene among the HGF-X genes in terms of gene expression efficiency, and it effectively expresses both HGF isoforms. (C)

[redacted]

(C)

15 bp

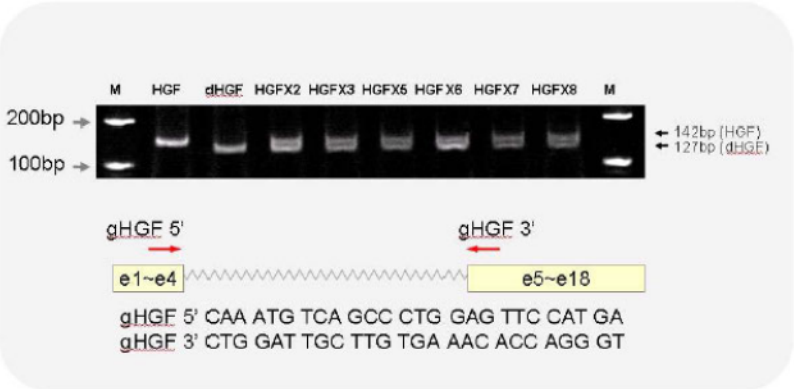
VM202

[redacted]

[redacted]

[redacted]

[redacted]



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8. Study objective and hypothesis

8.1 Objective

The purpose is to evaluate the following two aspects of the treatment method involving direct myocardial injection of VM202RY into reversible coronary artery regions where complete reperfusion cannot be achieved by coronary artery bypass surgery.

(a) Safety

(b) Preliminary efficacy

: Determination of the optimal dosage through dose escalation and verification of therapeutic effects

8.2 Hypothesis

Direct myocardial injection of VM202RY during coronary artery bypass surgery in areas of incomplete reperfusion is a safe treatment method.

9. Investigational product

9.1 Composition, dosage, and formulation of the investigational product

Item	Investigational prodcuct
Content	pCK-HGFX7
Code	VM202RY
Formulation and appearance	White cake lyophilized and packaged in vials
Ingredients and contents	2mg/vial of lyophilized hepatocyte growth factor gene with 44mg sucrose and 36mg NaCl as DNA stabilizers
Dosage	• Preparation for administration: After CABG procedure, VM202RY (2mg/1 vial) is dissolved in 4mL of sterile distilled water, left at room temperature for 5 minutes to completely dissolve, and then placed in a 1mL sterile syringe (27G) and injected intramuscularly. • Administration dose: ◦ Cohort 1: intramuscular injection of 1 mL out of 4 mL VM202 RY ◦ Cohort 2: intramuscular injection of 2 mL out of 4 mL VM202 RY ◦ Cohort 3: intramuscular injection of 4 mL out of 4 mL VM202 RY
Storage	2 ~ 8℃

9.2 Packaging of investigational product

The VM202RY used in the clinical trial was manufactured by Strathmann Biotec (Germany). VM202RY (2 mg/1 vial) is labeled and provided to the clinical pharmacist.

9.3 Labeling of investigational product

The container or packaging label of the investigational drug used in the clinical trial shall include the following information as specified by KGCP:

- Subject number
- Indication that it is "For Clinical Trial Use"
- Product code name or the generic name of the active ingredient
- Lot number and expiration date or retest date
- Storage conditions
- Name of the manufacturer or importer of the drug
- Statement: "Not for use outside of the clinical trial"

9.4 Information on transport and storage of investigational product from the manufacturing site to the clinical trial site

9.4.1 Transport from the manufacturing site to the clinical trial site and quality inspection immediately after transport

VM202RY is delivered to the pharmacy of Seoul National University Hospital by air shipment, without X-ray screening at customs in Germany and South Korea, via biopharmaceutical import and delivery specialists (e.g., World Courier, TNT), and is maintained under refrigerated conditions (2℃–8℃) throughout transport by Strathmann Biotec AG.

Upon arrival at the pharmacy of Seoul National University Hospital, the clinical trial manager from ViroMed Co., [redacted] visually inspects the packaging condition, lyophilized state, and temperature conditions during transit. If no abnormalities are found, the VM202RY vials are stored in a refrigerator (2℃–8℃) at the pharmacy and used for the clinical trial.

The quality control (stability test) of the imported investigational product VM202RY is conducted in accordance with the stability testing criteria and methods submitted with the clinical trial application. Upon completion of the stability test, the results are reported to and filed with both the Korea Food and Drug Administration (KFDA) and the Clinical Trials Center Pharmacy at Seoul National University Hospital.

Since biologically active substances must be shipped only after coordination between the sender (sponsor), the carrier, and the recipient (investigator/site), the sender must follow the guidelines below to ensure safe and timely transportation:

- Comply with domestic and international shipping regulations.
- Ensure communication between the carrier and the recipient for smooth transport and receipt.
- Prepare the necessary shipping labels and declaration forms.
- Take steps to ensure prompt delivery.
- Send all relevant shipping documents to the receiving laboratory or facility.

9.4.2 Storage

VM202RY must be stored at a temperature of 2℃ to 8℃, and refrigeration equipment capable of maintaining this set temperature must be used during storage. The refrigeration unit used to store VM202RY must be equipped with a locking mechanism, and temperature fluctuations and the condition of the refrigeration system must be carefully monitored and managed.

9.4.3 Retest date

The stability testing of the VM202RY investigational product (manufactured by Strathmann Biotec, Germany) will be conducted for 36 months from the start of the stability study, in accordance with the retest dates listed in the clinical trial application. The test result reports for each retest date will be kept on file at ViroMed Co., Ltd. and the Seoul National University Hospital Pharmacy.

Time point	Off storage date	Number of vials/storage temperature		Number of vials per time point
		-20°C	5°C	
0 months	16 March 2006	-	-	Release
1 month	16 April 2006	3	3	6
3 months	16 June 2006	3	3 + 11	17
6 months	16 September 2006	3	3	6
12 months	16 March 2007	3	3 + 11	17
18 months	16 September 2007	3	3	6
24 months	16 March 2008	3	3 + 11	17
36 months	16 March 2009	3	3	6

In addition, prior to the production of the clinical trial lot, a separate stability test was conducted according to the schedule below using the same formulation of the drug produced by TaKaRa Bio (Japan).

Stability test schedule	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted] stability testing beyond the planned 36-month stability testing period will be conducted in accordance with the stability testing standards and methods submitted in the clinical trial application, as follows:

If subject enrollment is completed before June 2009, stability testing will be performed on June 16, 2009.

If enrollment is completed before September, testing will be conducted on June 16 and September 16.

If enrollment is completed before December, testing will be conducted on June 16, September 16, and December 16.

These tests will be performed using the imported clinical trial VM202 final products stored at the Clinical Trials Center Pharmacy of Seoul National University Hospital. Upon completion of the stability tests, the results will be reported to and filed with the Korea Food and Drug Administration and the Clinical Trials Center at Seoul National University Hospital.

[redacted]

9.5 Management and documentation of investigational products

The pharmacist responsible for managing the investigational product used in the clinical trial must confirm in writing and sign the receipt and quantity of the investigational product provided by the sponsor.

Dispensation of the investigational product must be carried out based on a prescription signed by the principal investigator or sub-investigator participating in the study. The drug accountability log must record the patient's English initials, subject ID number, prescription date, and quantity dispensed.

Any unused investigational product after preparation must be returned to the pharmacist in its original vial, and the pharmacist must record the details in the drug accountability log.

The clinical trial monitor will regularly check the inventory of investigational products held by the pharmacist to verify proper usage of all trial drugs.

Upon completion or early termination of the clinical trial, the handling or return of unused investigational products shall be in accordance with the sponsor's instructions.

Under no circumstances may the investigator supply the investigational product or related materials to other investigators or institutions or use them for purposes not specified in the clinical trial protocol, without prior approval from the sponsor.

10. Indication

This trial targets all patients undergoing coronary artery bypass graft (CABG) surgery, specifically those in whom incomplete revascularization is anticipated due to poor vascular condition in areas with reduced myocardial perfusion, making vascular anastomosis unfeasible during surgery

11. Subject Inclusion Criteria, Exclusion Criteria, Target Number of Subjects, and Their Rationale

11.1 Inclusion criteria

1. Patients aged between 19 and 75 years (inclusive).
2. Patients whose myocardial SPECT scan of the coronary artery region shows a decrease in perfusion of 7% or more in the stress image compared to the resting image.
3. Patients for whom coronary angiography shows either a coronary artery diameter of 1 mm or less, diffuse atherosclerosis, or severe calcification, and who are thus considered to have a potential for incomplete revascularization during surgery, or for whom coronary artery bypass surgery is judged to be infeasible in some myocardial perfusion areas.
4. Patients who, prior to the start of the clinical trial, have provided written informed consent either themselves or through a legal representative, and who are able to comply with the requirements of the clinical trial.

11.2 Exclusion criteria

Patients who meet any of the following criteria will not be eligible to participate in this clinical trial:

1. Patients with ongoing heart failure or symptomatic heart failure (Killip class II or higher, or left ventricular ejection fraction < 25% on echocardiography).
2. Patients with uncontrolled ventricular arrhythmia on ECG or a history of treatment for ventricular arrhythmia.
3. Patients with current or a history of malignant tumors.
4. Patients with current serious infectious diseases.
5. Patients with uncorrected hematologic disorders.
6. Patients requiring concomitant valvular surgery or left ventricular volume reduction surgery.
7. Patients with current or a history of proliferative retinopathy.
8. Patients with severe comorbidities expected to cause death within 1 year (i.e., during the clinical follow-up period).
9. Patients with a history of drug or alcohol abuse within the past 3 months.
10. Pregnant or breastfeeding women, and women of childbearing potential who have not reached menopause. However, women who have undergone surgical sterilization procedures such as hysterectomy or bilateral tubal ligation may participate in the trial. Even if a woman agrees to use contraception, she may not be enrolled in the trial unless surgically sterilized.

11. Patients deemed inappropriate for clinical trial participation by the investigator.
12. Patients with cerebrovascular disease (e.g., current or within the past 6 months: cerebral infarction, cerebral hemorrhage, or transient ischemic attack).
13. Patients diagnosed with essential hypertension according to JNC VII whose blood pressure is not controlled with medication.
14. Patients with severe hepatic impairment (including those with AST or ALT levels ≥ 2 times the upper limit of normal [currently 40 IU/L] before administration of the investigational drug).
15. Patients with severe renal impairment (including those with serum creatinine > 2 mg/dL, anuria, acute renal failure, or those undergoing dialysis before administration of the investigational drug).
16. Patients who have undergone coronary artery bypass graft (CABG) surgery.
17. Patients who have undergone vascular angioplasty within 1 year prior to enrollment in this clinical trial.

11.3 Intraoperative confirmation for subject enrollment

1. Eligible if the target coronary artery travels intramyocardially and cannot be dissected.
2. Eligible if the condition of the vessel prevents partial anastomosis.
3. Excluded if hemodynamic instability makes the use of cardiopulmonary bypass during surgery unavoidable.
4. Excluded if, despite preoperative findings showing a coronary artery diameter of 1 mm or less, diffuse atherosclerosis, or severe calcification, vessel anastomosis is found to be feasible during surgery.

Among the above criteria, a subject may be enrolled if either condition 1 or 2 is met.

11.4 Target number of subject and rationale

The Phase I, single-center, open-label, dose-escalation study, which precedes a Phase II clinical trial, is intended to explore safety and determine the appropriate dosage. Since the nature of this clinical trial is not to test statistical hypotheses, it is desirable to conduct the study with the minimum number of subjects necessary to meet its objectives.

Therefore, this clinical trial will assign 3 subjects to each dose group. If dose-limiting toxicity (DLT) occurs during the trial, up to a maximum of 18 subjects may be enrolled. The goal is to conduct a 6-month follow-up after surgery. If any subjects drop out during the follow-up period, additional subjects will be recruited to ensure that 3 subjects per group complete all 6 months of the trial.

However, dose escalation will be discontinued if DLT occurs in 2 out of the 3 patients in any dosing group, or if any patient develops cancer or proliferative retinopathy attributable to the VM202RY gene therapy.

12. Clinical trial duration

The clinical trial is expected to last approximately 38 months, starting from the date of approval of the clinical trial protocol by the Minister of Food and Drug Safety until the completion of the last subject's participation.

The 38-month trial period includes approximately 128 weeks for subject recruitment and approximately 152 weeks for follow-up of the last subject.

13. Clinical trial design

13.1 Overall clinical design

This study is a Phase I clinical trial investigating the improvement of myocardial perfusion and contractility through the intramyocardial injection of VM202RY into areas of incomplete revascularization during coronary artery bypass grafting (CABG).

All patients scheduled to undergo CABG are considered potential candidates for screening. Subjects who provide written informed consent will undergo all required screening assessments within 21 days prior to surgery (Day 0). However, for coronary artery disease-related tests such as MIBI SPECT, MRI, TTE, ECG, and Holter monitoring, results conducted within 21 days before gene administration may be used. For coronary angiography (CAG), results from within 3 months prior to screening may be accepted.

If, during surgery, a coronary artery is found to be in such poor condition that vessel anastomosis is not feasible—thus resulting in incomplete revascularization—VM202RY will be injected intramyocardially at 4 or 8 sites in the affected region.

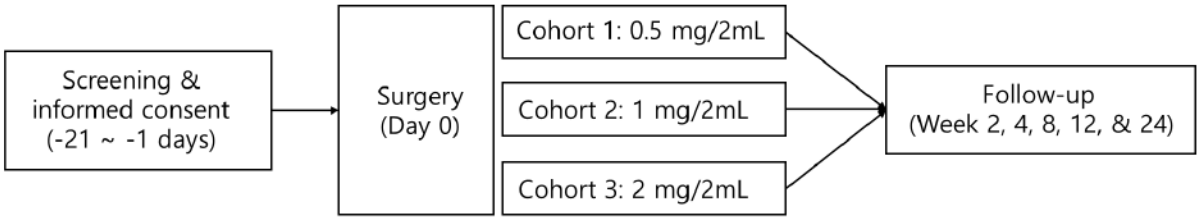
The concentrations of VM202RY will differ by cohort as follows:

- Cohort 1: 0.5 mg/1 mL
- Cohort 2: 1 mg/2 mL
- Cohort 3: 2 mg/4 mL

Three subjects per group will complete the trial, starting with the lowest dose group and proceeding to higher dose groups, in order to evaluate the safety and therapeutic effect of VM202RY.

Subjects will be hospitalized for 7 days to receive gene therapy. Follow-up visits will take place at 2-, 4-, 8-, 12-, and 24-weeks post-surgery (Day 0), during which follow-up assessments will be performed, and any adverse events or concomitant medications will be reviewed.

A summary of the study design is provided below.



13.2 Visiting schedule outline

13.2.1 Screening

Screening will be conducted for patients scheduled to undergo coronary artery bypass graft (CABG) surgery, starting from 21 days prior to surgery up to the day before surgery. During this period, written informed consent for participation in the clinical trial will be obtained, and all screening-related tests will be performed.

However, for coronary artery disease-related tests—such as MIBI SPECT, MRI, TTE, ECG, and Holter monitoring—previous results may be used if the tests were conducted within 21 days prior to gene administration. For coronary angiography (CAG), results may be used if the test was performed within 3 months prior to screening.

13.2.3 Follow-up

Subjects must return for follow-up assessments at 2, 4, 8, 12, and 24 weeks after the date of surgery (Day 0).

- For the 2- and 4-week visits, the visit window period is ±4 days from the scheduled visit date.
- For the 8-, 12-, and 24-week visits, the visit window period is ±7 days from the scheduled date.

Additionally, regardless of the results of this clinical trial, follow-up monitoring for major adverse events—such as the development of cancer and survival status—will be conducted at 1, 2, 3, 4, and 5 years after VM202RY administration. If in-person visits are not possible, telephone follow-ups may be conducted. These follow-up checks must occur annually from the date of investigational drug administration, within a ±30-day window.

The sponsor must report the results of each year's follow-up to the Ministry of Food and Drug Safety (MFDS), and any serious adverse events related to the drug must be reported to the MFDS promptly, even if they occur during the long-term follow-up period.

13.3 Allocation method for study cohorts

To evaluate the safety and determine the appropriate therapeutic dosage of VM202RY administered via intramyocardial injection during coronary artery bypass graft (CABG) surgery, the study will be conducted using the following three groups:

(1) Cohort 1

VM202RY 0.5 mg/1 mL will be injected into 4 sites (0.125 mg/0.25 mL per injection point) within the area of incomplete revascularization after CABG.

(2) Cohort 2

VM202RY 1 mg/2 mL will be injected into 8 sites (0.125 mg/0.25 mL per injection point) within the area of incomplete revascularization after CABG.

(3) Cohort 3

VM202RY 2 mg/4 mL will be injected into 8 sites (0.25 mg/0.5 mL per injection point) within the area of incomplete revascularization after CABG.

This clinical trial is an open-label study. It will begin with the lowest dose group, followed by a 4-week follow-up to evaluate safety and therapeutic effect before proceeding to the next higher dose group.

Subjects will be enrolled in the order in which they provide informed consent. To ensure safety, subjects within the same dose group will not undergo CABG and gene therapy at the same time. That is, in each dose group, the gene therapy for the next subject will begin only after the previously enrolled subject has undergone gene therapy and follow-up evaluation has commenced.

The estimated overall duration of the clinical trial is outlined in the following table

	CABG & gene therapy										
		Follow-up									
Day	4 months			4 months			4 months				
Cohort 1 (0.5 mg)	Screen	Treatment	Safety review		End of study						
Cohort 2 (1 mg)				Screen	Treatment	Safety review		End of study			
Cohort 3 (2 mg)							Screen	Treatment	Safety review		End of study

Long-term follow-up will be managed separately from the results of this clinical trial.

13.4 Preparation, dosage, administration method, and handling of the investigational product used in the clinical trial

13.4.1 Dilution method and dosage of VM202RY for intramyocardial injection in each cohort

1. After CABG surgery, VM202RY 2 mg (1 vial) is dissolved in 4 mL of sterile distilled water and left at room temperature for 5 minutes to completely dissolve. Then, 1 mL is drawn into a sterile syringe (27G) and immediately administered via intramyocardial injection.
2. In Cohort 1, using one 1 mL sterile syringe (27G), one-quarter of the VM202RY 2 mg dissolved in 4 mL sterile distilled water (0.5 mg/1 mL) is divided and injected into 4 sites (0.125 mg/0.25 mL per injection point).
3. In Cohort 2, using two sterile syringes (27G), half of the VM202RY 2 mg dissolved in 4 mL sterile distilled water (1 mg/2 mL) is divided and injected into 8 sites (0.125 mg/0.25 mL per injection point).
4. In Cohort 3, using four 1 mL sterile syringes (27G), the entire VM202RY 2 mg/4 mL dissolved in sterile distilled water is divided and injected into 8 sites (0.25 mg/0.5 mL per injection point).

13.4.2 Coronary artery bypass grafting (CABG)

1. Standardized Method: Under general anesthesia, pulmonary artery pressure is monitored using transesophageal echocardiography and a Swan-Ganz catheter. After median sternotomy, the left internal mammary artery and right gastroepiploic artery or right internal mammary artery are harvested using a skeletonization technique. Heparin (150 U/kg) is administered intravenously. A composite graft is created by connecting the right gastroepiploic artery or right internal mammary artery to the side of the left internal mammary artery. The left anterior descending artery is anastomosed using a local stabilizer on a beating heart, followed by anastomosis to the branches of the left circumflex artery and right coronary artery territory. After completing the anastomosis, protamine (0.15 mg/kg) is administered for neutralization, and the patency of the anastomosis is checked using a flowmeter before completing the surgery.
2. Distinguishing the Bypass Site from the Gene Injection Site: Although not strictly necessary for safety evaluation, for future efficacy assessments, the entire myocardial region will be segmented and evaluated by echocardiography, myocardial SPECT, and cardiac MRI. Therefore, it is expected to be possible to distinguish the bypass site from the gene injection site. This distinction will be particularly useful for efficacy evaluation in subsequent Phase 2 and Phase 3 studies involving control groups.
3. Target Group: All study subjects will undergo the procedure on Day 0, with VM202RY injected into the distal portion of the myocardium showing incomplete revascularization.
4. The goal is to confirm patency on angiography performed before discharge after surgery.

5. Surgery will primarily be performed on a beating heart. Patients requiring cardiopulmonary bypass due to hemodynamic instability will be excluded.

13.4.3 VM202RY injection procedure

After completing coronary artery bypass grafting, VM202RY is injected directly into the distal portion of the vessels with incomplete revascularization as follows:

- Cohort 1: A total of 1 mL (0.125 mg/0.25 mL per injection) is injected at 4 sites—2 sites on each side of the vessel.
- Cohort 2: A total of 2 mL (0.125 mg/0.25 mL per injection) is injected at 8 sites—4 sites on each side of the vessel.
- Cohort 3: A total of 4 mL (0.25 mg/0.5 mL per injection) is injected at 8 sites—4 sites on each side of the vessel.

13.4.4 Post-injection care and monitoring

1. Closely monitor the injection sites for bleeding in the operating room.
2. Manage the patient as per standard coronary artery bypass grafting postoperative care.
3. After monitoring ECG and hemodynamic parameters in the intensive care unit and confirming there are no hemodynamic issues, remove the ventilator the next day and perform coronary angiography.

13.4.5 Expected complications from injection and management

1. Bleeding at the injection site is minimized by using a 27G needle. If bleeding occurs, avoid suturing if possible and control bleeding with local hemostatic agents such as Surgicel.
2. Ventricular arrhythmias following VM202RY injection are managed with medications such as lidocaine and amiodarone.

13.4.6 Basis for dose setting and dose escalation

1) Timing of dose escalation

(1) After observing patients receiving the same dose for 4 weeks (4 weeks after administration of the investigational drug), if the criteria for dose escalation discontinuation are not met, the dose will be increased to the next level.

Criteria for Discontinuing Dose Escalation

① Dose-limiting toxicity (DLT) occurs in 2 out of 3 patients.
② A patient develops cancer or proliferative retinopathy attributable to VM202RY gene therapy.
③ If DLT occurs in 1 out of 3 patients at the same dose, an additional 3 patients will be tested at that dose, and if DLT occurs in 1 out of these 3 additional patients (i.e., 2 out of 6 patients), dose escalation will be discontinued.

2) Additional subject enrollment

(1) If dose-limiting toxicity (DLT) occurs in 1 out of 3 patients, an additional 3 patients will be enrolled at the same dose level. If no DLT occurs in these additional 3 patients, dose escalation to the next level will proceed.
(2) If any subjects drop out during the follow-up period (24 weeks) within the same dose group, additional subjects will be enrolled to replace the dropouts.

3) Basis for dose setting

The dose was set based on the results of preclinical studies of VM202RY and the preclinical results conducted by Morishita's group, following the typical dose-setting criteria applied in Phase 1 clinical trials.

(1) Basis from toxicity study results

In toxicity tests using rats and mice, no toxic changes were observed even at doses of 13.68 mg/kg in repeated dose toxicity tests (400 times the maximum clinical dose of 2 mg/human), 6.84 mg/kg in single dose toxicity tests (200 times the maximum clinical dose), 1.14 mg/kg in immunotoxicity tests, and 6.84 mg/kg in genetic and reproductive toxicity tests (200 times the maximum clinical dose). These results suggest that the clinical doses of 0.5, 1, and 2 mg used in this clinical trial are safe, being at least 200 times and up to 400 times lower than the tested toxic doses.

(2) Basis from efficacy study results

In efficacy evaluations using a rabbit model of ischemic limb disease, intramuscular administration of VM202RY at 0.25 mg/kg showed significant increases in arteriole and microvascular density as well as blood flow. These findings were similar to the preclinical results reported by Morishita's group (Taniyama et al., Gene Therapy, 2001(8):181–189). In a rat model of ischemic heart disease, intramyocardial injection of VM202RY at 0.625 mg/kg resulted in improved cardiac ejection fraction, increased interventricular septal thickness, increased microvasculature at the injection site, and significant reduction in myocardial fibrosis. These results were comparable to Morishita's preclinical studies using HGF naked DNA mixed with liposomes, and showed superior effects compared to HGF naked DNA alone (Miyagawa et al., Circulation, 2002(105):2556–2561).

In a porcine ischemic heart disease model, intramyocardial injection of VM202RY at 0.033 mg/kg led to significant increases in perfusion within ischemic myocardium,

reduced ischemic myocardial wall thickening, improved cardiac ejection fraction, and increased microvasculature at the gene delivery site. The porcine intramyocardial dose of 0.033 mg/kg (1 mg/30 kg) corresponds to the maximum clinical dose of 2 mg/60 kg in this trial, where clear efficacy was confirmed.

Therefore, the three-step dosing regimen set for this clinical trial is expected to be safe and, based on these preclinical results, is also anticipated to have therapeutic effects in the clinical study.

(3) Determination of dose for phase 1 clinical trial

Typically, the initial dose in a Phase 1 clinical trial is selected with the highest priority on participant safety. According to the “Guidelines for Conducting Initial Clinical Trials” (Son Dong-ryul, 1993, Journal of Clinical Pharmacology), the initial dose should be one that is expected to produce no reaction in humans. Once the initial dose is determined, subsequent dose increases are made by doubling the dose stepwise until a drug effect appears, after which the dose is increased by 1.5 times the previous level or by multiplying the effective dose by an integer. Dose escalation continues until the dose is no longer tolerable, the desired effect is achieved, or adverse effects appear in some participants.

Unlike typical Phase 1 trials conducted in healthy volunteers or patients with mild diseases, this trial targets patients with severe cardiac disease. Therefore, based on preclinical results indicating no safety concerns and anticipated efficacy, it is considered reasonable to set the initial dose at a level expected to be both safe and effective.

Combining the above prior research results and commonly applied Phase 1 dose-setting principles, the initial dose of VM202RY is set at 0.5 mg for a 60 kg subject. This dose corresponds to approximately 1/800th of the maximum dose (6.84 mg/kg) from rat single-dose toxicity tests where no toxicity was observed. Subsequent dose escalations will be made by doubling the previous dose if no safety issues arise, gradually increasing up to 2 mg/60 kg human (0.033 mg/kg; 1 mg/30 kg pig), which showed efficacy in a porcine ischemic heart disease model.

The maximum dose in this clinical trial, 2 mg/60 kg human, demonstrated efficacy in the porcine heart disease model, thus it is expected to be an effective dose of the investigational drug. It is therefore considered a necessary dose for observing the safety margin and therapeutic dose range.

13.5 Concomitant medications

13.5.1 Medications commonly used concomitantly during the clinical trial

1) Before surgery: nitrate, aspirin, clopidogrel, diuretics, beta-blockers, ACE inhibitors, Angiotensin II receptor blocker, heparin, statins, aldosterone antagonist, digitalis, antibiotics

2) During surgery: heparin, dopamin, dobutamin, nitrate, amiodarone, antibiotics, phenylephrine, vasopressin, protamine, lidocaine, beta-blcoker

3) After surgery: nitrate, dopamin, dobutamin, epinephrine, antibiotics, calcium channel blocker, nitrate, aspirin, clopidogrel, diuretics, beta-blockers, ACE inhibitors, Angiotensin II receptor blocker, statins, aldosterone antagonist, digitalis, antibiotics

Since this clinical trial involves patients with severe conditions, many concomitant medications will be administered before, during, and after surgery. The investigator must record the generic name, dosage, administration period, and indication of all medications given to the subjects during the clinical trial in the case report form.

13.5.2 Prohibited concomitant medications

There are no specific concomitant medications prohibited in this clinical trial.

14. Observation items, clinical test items, and observation/test methods

For detailed schedules of observation and test items, refer to the clinical trial flow chart.

14.1 Screening

1) Clinical evaluation

1. Medical history: diabetes, hypertension, stroke, hyperlipidemia, cardiovascular diseases, hematologic disorders, malignant tumors, trauma affecting the circulatory system, surgical history, smoking history, and other significant past medical history
2. Family history: diabetes, hypertension, stroke, hyperlipidemia, cardiovascular diseases, peripheral vascular diseases, hematologic disorders, malignant tumors, and other significant family medical history
3. Current and past medication history
4. Past treatments for ischemic heart disease
5. Symptoms and physical examination of ischemic heart disease: vital signs, auscultation findings, and other examination findings. Canadian angina class, New York Heart Association functional classification

2) Laboratory tests

Laboratory tests performed during screening must be conducted within 21 days prior to surgery. However, tests related to the diagnosis of coronary artery disease (MIBI SPECT, MRI, TTE, ECG, Holter monitoring) may be used if the results were obtained within 21 days before gene administration, and coronary angiography (CAG) results may be used if performed within 3 months prior to screening.

Additionally, blood samples for anti-HGF antibody and HGF protein will be collected before surgery, and the test results will be recorded in the case report form after the 24-week follow-up period is completed.

1. General blood tests: CBC with differential count, ESR
2. General chemistry tests: Admission battery including electrolytes, lipid battery, CRP
3. Serology tests: HBsAg, anti-HCV, anti-HIV
4. Coagulation tests: PT, aPTT, fibrinogen
5. Urinalysis
6. Urine pregnancy test (female patients only)
7. ECG
8. Myocardial enzymes: CK/CK-MB, LDH, Troponin I
9. Chest X-ray
10. Transthoracic echocardiography (TTE)
11. Coronary angiography
12. Myocardial SPECT and cardiac MRI
13. Holter monitoring (portable ECG)
14. Blood sampling for anti-HGF antibody and HGF protein: performed before surgery
15. Fundus photography
16. Tumor marker tests: CEA, PSA, alpha-fetoprotein, CA19-9, CA125; fecal occult blood test

14.2 Step 1: coronary artery bypass surgery and gene therapy period

During the gene therapy period (7 days), the subjects will be hospitalized for treatment.

1) Clinical evaluation

Symptoms of ischemic heart disease and physical examination: vital signs, auscultation findings, and other clinical examination findings. Canadian angina class, New York heart association functional classification

2) Laboratory test

(Note: The test results for anti-HGF antibodies and HGF protein in blood will be recorded in the case report form after the completion of the 24-week follow-up period.)

1. General Blood Tests

- Common Tests
  - Days 0, 1, 2, 5, and 7: CBC with differential count

– Days 1 and 7: ESR

• Additional tests by study group: None

2. General Chemistry Tests

– Days 1, 2, 5, and 7: Admission battery with electrolytes, lipid battery

– Days 1 and 7: CRP

3. Urinalysis: performed on Days 1, 5, and 7

4. ECG: follow-up on Days 0, 1, 2, 5, and 7

5. Cardiac Enzymes (CK/CK-MB, LDH, Troponin I): performed on Days 0, 1, 2, 5, and 7

6. Chest X-ray: performed on Days 0, 1, 2, 5, and 7

7. Echocardiography (TTE): performed on Day 7

8. Holter Monitoring: performed on Day 7

9. Blood Sampling for HGF Protein: performed on Day 7

(Tests on the day of surgery [Day 0] should be performed prior to the procedure.)

3) Intensive care and monitoring

1. Day of Surgery (POD#0 DAY): After surgery, the patient is transferred to the intensive care unit (ICU) with ventilatory support. The amount of bleeding is monitored through chest tubes inserted into the pericardium, mediastinum, and left and right pleural cavities in the operating room. Reoperation is considered in cases of significant bleeding (e.g., 500cc within 1 hour, 400cc/hr over 2 hours, or 300cc/hr over 3 hours). Continuous monitoring of systemic arterial pressure and pulmonary arterial pressure is performed. Medications (inotropics or vasodilators) and fluids are administered as needed based on hemodynamic status. Transient arrhythmias such as ventricular arrhythmias or atrial fibrillation are monitored via 24-hour ECG, and antiarrhythmic therapy (e.g., amiodarone) is administered if necessary. The patient's level of consciousness is assessed after awakening from anesthesia.

2. POD#1 DAY: If there is no bleeding and the hemodynamic status is stable, the ventilator is removed. Intravenous vasodilators are switched to oral medications. Continuous monitoring of systemic and pulmonary arterial pressure and ECG continues. Once hemodynamic stability is confirmed, the patient is transferred to the general ward and monitored with a 24-hour ECG.

3. POD#2 DAY: Under 24-hour ECG monitoring, the patient begins light physical activity in the ward. Chest tubes are removed if daily drainage is less than 1cc per kg of body weight.

4. POD#3 ~ 6 DAY: While continuing 24-hour ECG monitoring, physical activity is gradually increased in the ward. The patient is observed for allergic reactions possibly related to gene therapy, such as skin rashes, angioedema, or bronchospasm.

5. POD#7 DAY: Holter monitoring is performed, and transthoracic echocardiography is conducted to evaluate cardiac function. If no abnormalities are found, discharge is considered.

14.3 Step 2: follow-up period

1) Follow-Up Assessment Schedule

A total of 24 weeks of follow-up evaluations will be conducted. Based on the day of surgery (Day 0), follow-up visits will occur at Weeks 2, 4, 8, 12, and 24. The visit window will be ±4 days for Weeks 2 and 4, and ±7 days for Weeks 8, 12, and 24.

2) Clinical Evaluation

1. Assessment of medication status
2. Evaluation of symptoms and physical examination related to ischemic heart disease: vital signs, auscultation findings, and other clinical signs; Canadian Cardiovascular Society (CCS) classification; New York Heart Association (NYHA) functional classification

3) Laboratory tests

(Note: The results of anti-HGF antibody and HGF protein levels in blood will be recorded in the case report form after completion of the Week 24 follow-up period.)

1. Complete Blood Count: CBC with differential count, ESR: Performed at Weeks 2, 4, 12, and 24.
2. General Chemistry Tests: Admission battery with electrolytes, lipid battery, CRP: Performed at Weeks 2, 4, 12, and 24.
3. Urinalysis: Performed at Weeks 2, 4, 12, and 24.
4. Cardiac Enzymes: CK, CK-MB, LDH, Troponin I: Performed at Weeks 2, 4, 12, and 24.
5. Chest X-ray: Performed at Weeks 2, 4, 12, and 24.
6. ECG: Performed at Weeks 2, 4, 8, 12, and 24.
7. Echocardiography (TTE): Performed at Weeks 12 and 24.
8. Coronary Angiography (CAG): Performed at Week 24.
9. Myocardial SPECT and Cardiac MRI: Performed at Weeks 12 and 24.
10. Blood Sampling for Anti-HGF Antibody: Performed at Weeks 2, 4, and 24.
11. Blood Sampling for HGF Protein: Performed at Weeks 2, 4, 8, 12, and 24. If two consecutive results are negative, testing will be discontinued, and results will be considered negative.
12. Holter Monitoring: Performed at Weeks 2, 4, 12, and 24.
13. Fundus Photography: Performed at Weeks 2, 4, 12, and 24.
14. Tumor Marker Tests (CEA, PSA, alpha-fetoprotein, CA19-9, CA125) and Fecal Occult Blood Test: Performed at Weeks 12 and 24.

14.4 Step 3: long-term follow-up

Long-term follow-up will be conducted to monitor for serious adverse events such as cancer occurrence and survival status at 1, 2, 3, 4, and 5 years after administration of VM202RY. If in-person visits are not possible, follow-up may be conducted via telephone. The timing of each visit should occur at one-year intervals from the date of investigational drug administration, within a ± 30-day window. The sponsor shall report the annual telephone follow-up results to the Ministry of Food and Drug Safety (MFDS) each year. Additionally, any serious adverse events related to the investigational drug that occur during this period must be promptly reported to the MFDS.

15. Adverse events ad precautions for use of VM202RY

Various methods have been attempted to deliver the therapeutic gene to the target myocardium, but none have yet secured a definitive advantage. Therefore, this research team aims to evaluate the safety of VM202RY by directly injecting it into the myocardium after performing standard coronary artery bypass graft (CABG) surgery. The target patients are those who are candidates for CABG and are expected to benefit most from gene therapy—specifically those with reversible myocardial regions or areas with incomplete reperfusion due to issues with the target coronary artery or graft vessels during surgery.

To date, no adverse effects have been reported in preclinical or clinical studies indicating that injection of the hepatocyte growth factor gene into the myocardium—or similar gene therapies—has a direct negative impact on CABG procedures

16. Discontinuation and withdrawal of subjects from the clinical trial

16.1 Criteria for discontinuation and treatment/safety measures

Subjects who have agreed to participate in this clinical trial may be withdrawn from the study under the following circumstances:

1. If it is newly determined that the subject does not meet the inclusion/exclusion criteria
2. If the subject exhibits hypersensitivity reactions to the investigational product
3. If it becomes difficult to continue the trial due to evident adverse effects
4. If clinical deterioration or death occurs, making it difficult to proceed with the trial
5. If, in the investigator's judgment, continued participation in the trial may be harmful to the subject

However, if any of the above conditions occur post-surgery, and it is difficult to distinguish them from the natural progression of the disease, the subject may continue to be included in the study for ongoing observation, and appropriate measures will be taken as needed.

16.2 Criteria for subject withdrawal and treatment/safety measures

Subjects who have agreed to participate in this clinical trial may be withdrawn from the study under the following circumstances:

1) If it is newly determined that the subject does not meet the inclusion/exclusion criteria
2) If recurrent myocardial infarction occurs before the initiation of coronary artery bypass grafting (CABG) and intramyocardial gene therapy
3) If clinical deterioration or death occurs before the initiation of CABG and intramyocardial gene therapy
4) If, during the treatment or follow-up period, the subject takes medications or consumes excessive alcohol that may affect the clinical outcome evaluation
5) If the subject no longer wishes to continue treatment
6) If the subject does not comply with the instructions of the principal investigator or sub-investigator, or misses two or more scheduled follow-up visits
7) If, in the judgment of the investigator, continued participation in the clinical trial may be harmful to the subject

If a subject is withdrawn or discontinues participation during the clinical trial, the investigator shall make every effort to provide standard clinical care. The sponsor shall provide compensation in accordance with the subject compensation policy, if applicable.

All such situations must be documented in the subject's Case Report Form (CRF) and source documents. For subjects who discontinue early, the reason for early termination must be recorded in the clinical trial completion section of the CRF, and tests and follow-up visits scheduled for the final visit should be conducted as much as possible.

Even if a subject discontinues early, previously collected test results may still be used for analysis, and additional subjects may be enrolled in the trial to compensate for those who drop out.

17. Statistical analysis methods

17.1 Evaluable subjects

In this study, all subjects who participated and received at least one dose of the investigational drug (including those who dropped out) will be included in the analysis.

17.2 Handling of data from subjects who drop out

If a subject drops out during the study, the analysis will be conducted based only on the data obtained up to the point of dropout.

17.3 Primary endpoint: safety

17.3.1 Safety evaluation population

Subjects who have been administered the investigational drug will be included, regardless of protocol violations or adherence to visit schedules. This clinical trial is designed to evaluate safety over a 6-month period.

17.3.2 Safety evaluation items

1) Dose Limiting Toxicity (DLT) assessment
2) Tolerated Dose (TD) assessment
3) Adverse reactions, vital signs, physical examination, and laboratory test results
4) Major Adverse Cardiovascular Events (MACE)
5) Safety assessment of VM202RY intramuscular injection

17.3.3 Safety evaluation methods and criteria

1) DLT (Dose Limiting Toxicity)

   Dose Limiting Toxicity (DLT) is evaluated from the first day of investigational drug administration up to 4 weeks post-administration. DLT is defined as adverse reactions of Grade 3 or higher according to the WHO Toxicity Scale, or severe adverse reactions classified as Grade 3 by Spilker's three-tier classification method, excluding adverse reactions associated with coronary artery bypass grafting (CABG).

Adverse reactions specific to CABG caused by the surgery itself are excluded from the DLT evaluation.

1. Blood test findings (in cases recovered without complications)

   (1) Hemoglobin: 8-17

   (2) WBC: 4-25

   (3) Platelet: 50-550

   (4) Bilirubin: 0.3-10.6

   (5) GOT/GPT: 9-125/8-350

(6) Alk. Phosphatase: 35-180

(7) BUN/Cr: it depends on the patient's preoperative kidney function

2. Reoperation due to bleeding: occurs in 5-10% of cases.

3. Fever: A persistent fever above 39°C is rare unless pulmonary complications or infections occur. Therefore, a fever above 39°C lasting more than 24 hours is considered outside the range of common complications.

4. Infection: Mediastinitis occurs in 2-3% of cases.

5. Arrhythmia: Atrial fibrillation occurs in 20-30% of cases. Transient premature ventricular contractions (PVCs) are common, but the occurrence of multifocal PVCs is considered abnormal. Ventricular tachycardia and fibrillation may occur due to postoperative bleeding, myocardial dysfunction, or reperfusion injury in chronically ischemic areas. If these are clearly related to surgery, such as bleeding from the graft or cardiac tamponade, they are considered surgical complications. However, unexplained ventricular arrhythmias can occasionally occur. Recurrent ventricular arrhythmias are uncommon in patients discharged after surgery. If the patient had recurrent ventricular arrhythmias before surgery with a consistent pattern and interval, these are not considered caused by gene therapy, but follow-up with Holter monitoring is needed to track any changes.

6. Allergic reactions: Occasionally, skin rash or bronchospasm occur after contrast agent use for preoperative imaging tests (coronary angiography, CT, MRI). Skin rash, bronchospasm, or anaphylactic shock can also occur due to blood transfusion reactions before or after surgery. These reactions typically occur immediately after administration of the causative agent and can usually be distinguished from reactions caused by gene therapy. However, since gene therapy is administered during surgery, which often involves transfusions, distinguishing the cause can be difficult. It is important to identify parameters such as rash occurrence or increased airway resistance on the ventilator immediately after surgery or during surgery—especially before and after gene injection—to clarify causality.

Assessment of adverse reactions related to coronary artery bypass grafting (CABG)

1. If continuous bleeding occurs after surgery (500 cc in the first hour, 400 cc/hr for the first 2 hours, 300 cc/hr for the first 3 hours) requiring re-thoracotomy, and surgical findings reveal that the bleeding is not from the gene injection site but rather from side branches of the graft, anastomosis sites, or diffuse bleeding at the wound caused by antiplatelet agents used to prevent graft occlusion, this is considered a surgical complication rather than an adverse reaction to gene therapy.

2. In cases of postoperative mediastinitis, only if the sterile distilled water used to dissolve the gene tests positive in culture for the same pathogen isolated from the patient is the complication considered related to gene injection. Otherwise, it is determined to be an infection related to CABG.

3. If complications such as skin rash or bronchospasm occur after blood transfusion, antibiotic injections, or contrast-enhanced tests following surgery, these will be evaluated by an allergy specialist to determine any association with gene therapy. If no causal relationship with the administered gene is found, the reactions will be regarded as general adverse reactions related to CABG.

4. Other adverse reactions characteristic of CABG mentioned above will be classified as surgery-related complications.

Reactions due to surgery listed under WHO toxicity scale items

According to the WHO Toxicity Scale, toxicities of Grade 3 or higher are generally considered dose-limiting. However, since this clinical trial includes surgery, the following reactions caused by surgery are excluded from the DLT (Dose-Limiting Toxicity) evaluation:

Adverse events caused by coronary artery bypass graft (CABG) surgery are excluded from the DLT evaluation.

1. Hematology
   - Hemoglobin: Decrease due to surgical bleeding that recovers with transfusion.
   - Hemorrhage: Common post-operative complication. However, persistent bleeding at the gene injection site should result in discontinuation of dose escalation.
2. Gastrointestinal
   - Bilirubin: Elevation up to 10.6 due to intra-body retention of hematoma after surgery is considered a normal response.
   - GOT/GPT (AST/ALT): Levels up to 125/350 are excluded if attributable to transfusion or myocardial ischemia.
3. Renal / Bladder
   - Proteinuria: If caused by pre-existing diabetes or renal failure.
   - Hematuria: If caused by trauma during Foley catheter insertion.
4. Pulmonology: Findings due to decreased cardiac function.
5. Fever: Fever above 39°C lasting less than 24 hours (unless associated with pulmonary complications or infection).
6. Allergic Reactions: When the cause is clearly identified, such as contrast agents, antibiotics, or blood transfusion.
7. Cardiac
   - Rhythm: Arrhythmias are unavoidable due to surgical dissection of the myocardium. While ventricular arrhythmias may occur due to reperfusion of chronically ischemic areas, establishing a direct association with gene injection is difficult. However, in the interest of patient safety, WHO Grade 3 criteria will be followed and dose escalation will be discontinued.
   - Cardiac Function: Most patients have impaired cardiac function due to the nature of cardiac surgery; thus, excluded from DLT evaluation.
   - Pericarditis: Most cases involve post-operative accumulation of blood or fluid in the pericardial space. Surgery may be necessary, but dose escalation will be discontinued only if bleeding is confirmed at the gene injection site.

2) TD (tolerated dose) evaluation

Subjects are enrolled sequentially, starting from Step 1, to determine the tolerated dose as follows:

1. Step 1: Three subjects are enrolled. DLT (Dose-Limiting Toxicity) is evaluated 4 weeks after the third subject is dosed.
   1-1. If no DLTs occur in any of the 3 subjects (0/3) → Proceed to Step 2 and enroll 3 more subjects (A)
   1-2. If DLT occurs in 1 out of 3 subjects (1/3) → Enroll 3 additional subjects at the same dose
      1-2-1. If no DLTs in the additional 3 subjects (1/6) → Proceed to Step 2, enroll 3 more subjects (A)
      1-2-2. If 1 additional DLT occurs among the 3 (2/6) → Stop dose escalation
   1-3. If DLT occurs in 2 out of 3 subjects (2/3) → Stop dose escalation
2. Step 2: Three subjects are enrolled. DLT is evaluated 4 weeks after the third subject is dosed.
   2-1. If no DLTs occur in all 3 subjects (0/3) → Proceed to Step 3, enroll 3 more subjects (B)
   2-2. If DLT occurs in 1 out of 3 subjects (1/3) → Enroll 3 additional subjects at the same dose
      2-2-1. If no DLTs in the additional 3 subjects (1/6) → Proceed to Step 3, enroll 3 more subjects (B)
      2-2-2. If 1 additional DLT occurs among the 3 (2/6) → Stop dose escalation (A)
   2-3. If DLT occurs in 2 out of 3 subjects (2/3) → Stop dose escalation (A)
3. Step 3: Three subjects are enrolled. DLT is evaluated 4 weeks after the third subject is dosed.
   3-1. If no DLTs occur in all 3 subjects (0/3) → End of clinical trial (C)
   3-2. If DLT occurs in 1 out of 3 subjects (1/3) → Enroll 3 additional subjects at the same dose
      3-2-1. If no DLTs in the additional 3 subjects (1/6) → End of clinical trial (C)
      3-2-2. If 1 additional DLT occurs among the 3 (2/6) → End of clinical trial (B)
   3-3. If DLT occurs in 2 out of 3 subjects (2/3) → End of clinical trial (B)

Tolerated dose

Condition	Tolerated dose
A + B + C	C
A + B	B

A	A

3) Adverse events and laboratory test values

An adverse event is defined as any symptom, sign, or disease that occurs or worsens during the clinical trial, regardless of its relationship to the investigational drug. It is the responsibility of the investigator and study staff to record all adverse events that occur during the clinical trial. Adverse events should be recorded using medical diagnostic terminology; if that is not possible, terms describing observed symptoms and signs reported by the subject should be documented.

All adverse events, clinical laboratory test results, and vital signs (blood pressure, temperature, pulse, respiration) of the study subjects will be summarized in tables and reviewed comprehensively to assess dose-dependent trends. All clinically significant abnormal laboratory results should be recorded in the adverse event section of the case report form (CRF), and the severity, course, and relationship to the investigational drug must also be documented.

As the number of subjects assigned per dose group in a Phase I clinical trial is small, the determination of normal or abnormal laboratory test results will be made on a per-subject basis. Statistical validation may be performed if necessary. In particular, adverse events that are anticipated or listed in the precautions for use must be closely monitored for changes, and if observed, should be tabulated by dose group for comparative analysis.

① Since the test subjects have not previously been exposed to the investigational substance, pre-treatment allergy and anaphylaxis testing methods are considered not meaningful. In addition, as the vector was manufactured using kanamycin instead of ampicillin, skin testing is also deemed unnecessary. Furthermore, as the investigational agent is an angiogenic substance, skin testing may potentially induce angiogenesis in the skin and is thus discouraged.
② Although the concentration of HGF in the blood is expected to be minimal following intramyocardial injection, due to concerns about retinal neovascularization, fundoscopy will be performed before surgery and during the follow-up period to assess potential retinal lesions.
③ Cardiac MRI will be used to monitor for the development of intramyocardial hemangiomas.
④ The occurrence of ventricular arrhythmia will be monitored via continuous ECG during hospitalization and regular ECG during the follow-up period.

All adverse events and their severity by dose group will be presented, and incidence rates along with 95% confidence intervals will be estimated. If feasible, Fisher's Exact Test will be used for comparisons.

Vital signs (blood pressure, temperature, pulse, respiration) will be summarized with descriptive statistics by group and visit to evaluate trends. Physical examination findings will identify abnormal findings before and after administration, presented by group. For laboratory tests (general hematology and chemistry), descriptive statistics will be provided by group and visit to observe trends. For urinalysis, changes from normal (pre-dose) to abnormal (post-dose) will be presented by group and visit to assess trends.

4) Major Adverse Cardiac Event (MACE)

In this study, MACE is defined as cardiac death, myocardial infarction, ventricular arrhythmia requiring treatment, or hospitalization for target vessel revascularization. Investigators must monitor and confirm the occurrence of MACE. Any MACE must be reported to the sponsor in accordance with serious adverse event reporting guidelines. Inter-group comparisons of MACE incidence will be analyzed using Fisher's Exact Test.

5) Safety assessment of VM202RY intramyocardial injection

The safety of VM202RY intramyocardial injection will be evaluated by monitoring for persistent bleeding, arrhythmia, and other complications. Investigators must closely observe subjects for these events following VM202RY administration. The incidence of persistent bleeding, arrhythmia, and other complications will be presented by treatment group, and inter-group comparisons will be performed using Fisher's Exact Test.

17.4 Secondary endpoint: efficacy

Although the primary objective of this Phase I clinical trial is to assess safety, considering that the subjects are severely ill patients and will be followed for a long period (6 months), it is deemed reasonable to also observe efficacy. Therefore, exploratory efficacy evaluation will be conducted as follows, only when such assessment is possible.

17.4.1 Efficacy evaluation population

Both Per-Protocol (PP) and Intention-to-Treat (ITT) analyses will be performed, and the target populations are as follows:

1) Subjects included in the Intention-to-Treat (ITT) analysis

Subjects who received the investigational product and for whom efficacy assessment is possible, regardless of protocol violations or adherence to visit schedules.

2) Subjects included in the Per-Protocol (PP) analysis

① Subjects who did not violate the inclusion/exclusion criteria (i.e., eligible patients)
② Subjects who completed administration according to the scheduled timing, method, and dosage
③ Subjects who were observed for at least 8 weeks after investigational product administration
④ Subjects with no missing data in the primary efficacy evaluation parameters
⑤ Subjects with no major protocol violations that could affect efficacy assessment (e.g., use of prohibited concomitant medications)

17.4.2 Efficacy evaluation parameters

1) Changes in cardiac function

2) Size of viable myocardium

3) Changes in the myocardial ischemic region

17.4.3 Methods and criteria for efficacy evaluation

1) Changes in cardiac function

Changes in cardiac function can be evaluated using the left ventricular ejection fraction (LVEF) measured by cardiac MRI, myocardial SPECT, and echocardiography. Differences between treatment groups before and after VM202RY administration will be tested using the Kruskal-Wallis test.

Cardiac MRI methods and criteria

Analysis will follow the standard cardiac MRI protocols of the Department of Radiology at Seoul National University Hospital, using an appropriate segment model based on the patient's heart size. Parameters evaluated will include left ventricular volume (mL), wall motion index, myocardial thickness (mm), and LVEF (%). Comparisons will be made between baseline and follow-up measurements for each patient, as well as between treatment groups.

Myocardial SPECT methods and criteria

A 20-segment model, similar to the MRI analysis, will be used. Blood flow in each coronary artery distribution area will be assessed using a Bull's-eye view. Perfusion (%) will be evaluated from stress and rest images obtained using Dipyridamole. Additionally, the degree of systolic wall thickening (%), left ventricular volume, and function over time will be compared between groups. Left ventricular volume (mL), ejection fraction (%), and cardiac output (mL) obtained from SPECT will be used as supplementary data. Wall motion indices before and after surgery will be compared. Criteria for determining perfusion deficits and reversibility will follow established standard methods.

Echocardiography methods and criteria

From transthoracic echocardiography, left ventricular diameter (mm), ejection fraction (%), and wall thickness (mL) will be measured and compared with follow-up results after surgery. The Wall Motion Score Index will be calculated by dividing the myocardium into 16 segments and assigning a score to each area based on motion: [1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic]. The total score for the entire myocardium and the right coronary artery region will be averaged by the number of segments.

2) Size of viable myocardium

Using cardiac MRI, the myocardial thickness at the gene injection site, the extent of late gadolinium enhancement, and local wall motion strength will be evaluated. Differences between groups before and after VM202RY administration will be tested using the Kruskal-Wallis test.

3) Improvement in Myocardial Ischemia

This will be assessed using myocardial SPECT (changes in blood flow in the gene injection region at rest and under stress). Group differences before and after VM202RY administration will be evaluated using the Kruskal-Wallis test.

17.5 Secondary endpoint: HGF plasma concentration

In typical phase 1 clinical trials, the pharmacokinetic characteristics of a drug are observed to assess the relationship between the administered dose, blood concentration, and any resulting clinical effects or adverse reactions. However, since the investigational product in this study is a gene therapy, it is not feasible or clinically meaningful to measure the conventional pharmacokinetic parameters used in standard phase 1 drug trials. Therefore, plasma HGF concentration will be measured and observed, and its correlation with the presence, severity, and pattern of adverse events will be evaluated.

17.6 Secondary endpoint: HGF antibody formation induced by VM202RY injection

The presence of HGF antibodies in the blood will be assessed using the ELISA method. A preliminary evaluation will be conducted to determine whether there is a correlation between HGF antibody formation and the improvement in myocardial function, by comparing subjects who showed improved cardiac function with those who did not.

18. Definition and reporting of adverse events

All adverse events that occur after the subject has signed the informed consent form must be recorded in the case report form (CRF). During the trial period, if the investigator becomes aware of any significant risk factors related to the safety of the investigational product, contraindicated concomitant medications, adverse events, or precautions for use, this information must be reported to the sponsor.

18.1 Definition of adverse events

An adverse event is defined as the occurrence or worsening of any of the following:

1) All symptoms and signs not related to the primary diagnosis, or symptoms and signs that are aggravated and related to the primary diagnosis

2) Clinically significant abnormalities in laboratory test results

3) Abnormal findings from physical examinations

These events must be recorded in the CRF even if they are not considered related to the investigational product (i.e., "possibly related" events should be recorded).

The investigator should assess adverse events according to the WHO Toxicity Scale. If the WHO scale is not applicable, the severity of adverse events should be evaluated using Spilker's three-grade classification system.

Grade	Criteria
Mild	When no treatment is required, and the subject's normal daily life (functions) is not significantly impaired
Moderate	When the subject's normal daily life (functions) is significantly impaired, treatment may be required, and recovery occurs after treatment
Severe	When a severe adverse reaction requires intensive medical intervention and leads to lasting aftereffects, or in cases of life-threatening adverse events

The investigator shall evaluate the causality between the adverse event and the investigational product based on the following criteria:

1) Definitely related

- There is evidence that the investigational product was administered.
- The temporal relationship between administration and the adverse event is appropriate.
- The adverse event is more likely explained by administration of the investigational product than by any other cause.
- The adverse event resolves upon discontinuation of the investigational product.
- The adverse event reappears upon rechallenge (if performed).
- The adverse event is consistent with known information about this product or products of the same class.

2) Probably related

- There is evidence that the investigational product was administered.
- The temporal relationship between administration and the adverse event is appropriate.
- The adverse event is more likely explained by administration of the investigational product than by other possible causes.
- The adverse event resolves upon discontinuation of the investigational product.

3) Possibly related

- There is evidence that the investigational product was administered.

- The temporal relationship between administration and the adverse event is appropriate.
- The adverse event is equally likely to be caused by the investigational product as by other possible causes.
- The adverse event resolves upon discontinuation of the investigational product (if done).

4) Probably not related

- There is evidence that the investigational product was administered.
- There is a more likely alternative cause for the adverse event.
- The adverse event does not resolve or shows an unclear outcome upon discontinuation (if done).
- The rechallenge result is negative or unclear (if done).

5) Definitely not related

- The subject did not receive the investigational product, or
- The temporal relationship between administration and the adverse event is not appropriate, or
- There is a clear alternative explanation for the adverse event.

If a dose-limiting toxicity (DLT) or an unexpected Grade 3 or higher adverse event occurs, the causality between the adverse event and the investigational product must be assessed by two or more investigators.

18.2 Classification of adverse events

1) Complications due to the natural progression of myocardial infarction: Arrhythmias, worsening of heart failure, recurrent myocardial infarction, and refractory angina.

2) Complications related to coronary artery bypass graft (CABG) surgery: Reoperation due to bleeding, perioperative myocardial infarction, fatal arrhythmias, stroke, infection, acute renal failure, atrial fibrillation, and early postoperative death associated with these complications.

3) Complications related to intramyocardial gene injection

- Side effects associated with gene injection: Extremely rare but may involve bleeding, which is controllable during surgery.
- Although serum HGF levels after intramyocardial injection are minimal, due to concerns about retinal angiogenesis, potential retinal lesions will be assessed via fundoscopy before and during the follow-up period after surgery.
- Development of hemangiomas in the myocardium will be monitored via cardiac MRI.
- The occurrence of ventricular arrhythmias will be monitored through continuous ECG monitoring during hospitalization and periodic ECG exams during the follow-up period.

4) Long-term adverse effects

- Worsening of underlying disease
- Progression of previously undetected malignant tumors
- Formation of heterotopic tissue within the heart (a theoretical possibility not yet empirically proven)

18.3 Serious adverse events

A serious adverse event is defined as any adverse event that, regardless of dose, results in any of the following:

1) Results in death or is life-threatening

2) Requires hospitalization or prolongation of existing hospitalization

   - Prolongation of hospitalization for patient convenience or non-clinical reasons is not considered a serious adverse event.

3) Results in persistent or significant disability/incapacity

4) Results in a congenital anomaly or birth defect

5) Although not immediately life-threatening, fatal, or requiring hospitalization, the event may jeopardize the subject based on appropriate medical judgment and may require medical or surgical intervention to prevent any of the outcomes listed above (e.g., allergic bronchospasm requiring emergency room or home intensive treatment, blood disorders not requiring hospitalization, seizures, drug dependence or abuse)

An unexpected adverse event refers to an event that is not described in the Investigator's Brochure, or is inconsistent in nature, severity, or frequency with the information provided therein.

18.4 Reporting regulations for adverse events

Any “serious” adverse event or Major Adverse Cardiac Event (MACE), regardless of predictability or its relation to drug use, must be reported immediately upon discovery using the Serious Adverse Event Report Form (provided by the sponsor) via phone or fax to the [redacted] which will be submitted to the sponsor and the Institutional Review Board (IRB).

However, serious adverse events occurring in subjects who discontinued the study after signing informed consent but before randomization, or after early termination of the trial, do not need to be reported to the IRB unless the investigator judges that the events were caused by the investigational drug or clinical trial procedures.

For all unexpected serious adverse drug reactions, ViroMed must promptly report to the Ministry of Food and Drug Safety (MFDS) with the investigator’s completed serious adverse event report, following the Adverse Event Reporting Guidelines (December 2000). The reporting deadlines are as follows:

- In cases resulting in death or life-threatening events, ViroMed must report within 7 days of becoming aware of the event, with detailed follow-up information submitted within 8 days of the initial report.

- For all other serious and unexpected adverse drug reactions, ViroMed must report within 15 days of awareness.

Separately from this clinical trial, the sponsor shall annually report the results of a 5-year follow-up telephone survey after VM202RY administration to the MFDS. Any unexpected serious adverse drug reactions occurring during this period must be promptly reported to the MFDS.

18.5 Follow-up management of adverse drug reactions

The principal investigator or responsible person must observe and document all adverse drug reactions related or possibly related to the investigational product that occur during the clinical trial period (from drug administration through follow-up). Monitoring should continue until the adverse reaction returns to baseline or normal levels, the investigator determines the reaction has resolved, or further observation is deemed unnecessary. Upon resolution of the adverse drug reaction, it must be reported to the MFDS. Whenever possible, the reason for discontinuation, treatment provided, and other course details should be investigated. If the subject does not visit in person, follow-up should be conducted via phone or mail.

19. Quality control and assurance of the clinical trial

Before the start of the trial, ViroMed staff, investigators, trial coordinators, and monitors will hold an Investigator's Meeting or Initiation Visit. Detailed discussions will be conducted on the protocol, trial procedures, case report form completion, and specimen collection methods.

Evaluators will receive appropriate training on assessment methods and tools during the Investigator's Meeting or Initiation Visit. Evaluators unable to attend prior training or joining later in the trial will receive training from the investigator or a designated person.

CMIC Korea and ViroMed will provide the trial sites with relevant guideline documents, and monitors will conduct monitoring according to those guidelines. Periodic site visits will be performed to compare source documents with case report forms and verify that the investigator conducts the trial according to the protocol and regulations, ensuring quality control. Communication with site investigators will also occur via mail, phone, and fax. After retrieving case report forms for subjects who have completed the trial, data review will be conducted.

All data will be verified by double data entry into the database. All source documents will be reviewed and corrections made to data entries. After data entry completion, logical checks will be run to identify inconsistent dates or lab test results outside normal ranges. All necessary database corrections will be documented in appendices or audit trails.

In addition to routine monitoring, audits will be performed to ensure the reliability of data collected in this clinical trial and to verify compliance with the protocol, standard operating procedures, Good Clinical Practice (GCP), and relevant regulations.

20 Direct access to source documents

To ensure the safety of participants and to obtain accurate, complete, and reliable data, the investigator must keep clinical test results, medical records, and other participant medical documents as source documents. The investigator must allow direct access to clinical trial-related data upon request by the sponsor, the Ministry of Food and Drug Safety (MFDS), and the Institutional Review Board (IRB).

21. Supply and handling of investigational product

To ensure proper management of investigational products used in the clinical trial, the following measures must be implemented:

1) Emphasize responsibility for managing the investigational products at the initial training meeting.

2) Provide a drug receipt and disposition log for the investigational products to be filed.

3) The monitor shall verify the drug receipt and disposition records for the investigational products used in the trial.

The investigator or designated pharmacist is responsible for explaining the correct use of the investigational product to the subjects, ensuring compliance with the guidelines, and maintaining accurate records of investigational product administration and retrieval.

22. Compensation policy for trial-related injury

If a subject is harmed as a result of participation in the clinical trial, ViroMed Co., Ltd. will provide compensation according to the compensation policy. Refer to Appendix 3 for the compensation policy details.

23. Post-trial medical care and treatment standards

Medical care and treatment of subjects after the conclusion of the clinical trial shall follow the general standards for patients who have undergone coronary artery bypass surgery.

24. Measures to protect subject safety

This clinical trial will be conducted scientifically and ethically according to Good Clinical Practice (GCP) and relevant laws and regulations. The trial will be conducted in accordance with the Declaration of Helsinki, respecting human dignity and rights, ensuring no

disadvantage occurs to the subjects. The Institutional Review Board will evaluate and approve the clinical trial protocol according to GCP and will regularly assess whether the trial is conducted according to the approved protocol.

Before enrolling subjects, the investigator must confirm each subject's health status to determine eligibility for participation. The investigator will be thoroughly familiar with the investigational drug and will make every effort to ensure the subjects' safety. If an adverse reaction occurs during the trial, appropriate medical care will be provided until the patient recovers. ViroMed will compensate for any damage caused by the investigational drug according to the compensation policy.

25. Other requirements for conducting the clinical trial safely and scientifically

25.1 Approval by the institutional review board (IRB)

This trial must be conducted ethically and scientifically and must obtain approval from the Institutional Review Board before the start of the clinical trial in accordance with KGCP.

25.2 Patient informed consent form and consent document

Before enrolling patients in the clinical trial, the investigator must provide sufficient information according to the Declaration of Helsinki (see Appendix 2) and KGCP, and obtain written informed consent (see Appendix 4).

The Institutional Review Board shall review the patient informed consent document that the investigator intends to use. It is the investigator's responsibility to obtain informed consent from the patient or their legal representative prior to initiating any procedure or treatment that is not part of routine clinical care

25.3 Monitoring

Monitors will conduct visits to the study sites to oversee the progress of the trial. The investigator must agree to and cooperate with providing monitors or their delegates access to the investigational product preparation and storage areas, as well as all trial-related documents. Additionally, if the Ministry of Food and Drug Safety conducts inspections or if the sponsor performs audits, the investigator must agree to and cooperate with these activities.

25.4 Case report form (CRF)

Source documents refer to the patient records maintained by the investigator at the trial site. Most source documents are hospital or investigator charts, and in such cases, all information

collected and recorded in the patient's Case Report Form must be consistent with the corresponding chart.

It is the investigator's duty to record, review, and sign the Case Report Form. By signing each completed Case Report Form, the investigator certifies that the information recorded is accurate. The investigator holds ultimate responsibility for the accuracy and reliability of all clinical and laboratory data recorded in the Case Report Form.

A copy of the Case Report Form must be kept in the investigator's file. All answers to queries must be written using a black pen. If any item in the Case Report Form cannot be recorded for any of the following reasons, the corresponding abbreviation should be used:

- Not applicable: NA (Not available or Not applicable)
- Test not performed: ND (Not done)

Dates must be recorded numerically in the order of year, month, and day (e.g., May 30, 2006 as 2006/5/30).

If data recorded in the original Case Report Form must be corrected or supplemented, the following method must be followed: draw a single line through the data to be corrected (do not erase or use correction fluid), so that the original entry remains readable. Then, rewrite the corrected data in black pen, and sign and date the correction; provide a reason for the correction if necessary.

The procedure for submitting Case Report Forms to ViroMed Co., Ltd. will be explained by the clinical trial monitor to the responsible personnel at the trial site.

Monitors designated by ViroMed Co., Ltd. will regularly visit the trial site at appropriate intervals to compare the Case Report Forms with the source documents. For this purpose, the investigator must agree to and cooperate with the monitor's access to the source documents.

Once data to be recorded are obtained, the Case Report Form should be completed as promptly as possible. Completed Case Report Forms will be collected by the monitor.

25.5 Retention of clinical trial related documents

The head of the clinical trial site shall retain all documents related to the trial, including reports submitted to the Ministry of Food and Drug Safety, the Institutional Review Board, and BiiV Healthcare.

In accordance with the Pharmaceutical Affairs Act Enforcement Regulations, the head of the clinical trial site shall appoint a person responsible for preserving the records and documents received from the IRB and the investigator. These documents must be retained for 10 years after the trial completion date or after the discontinuation of the development of the investigational product, and measures must be taken to prevent premature damage or loss due to accidents.

25.6 Amendments to the clinical trial protocol

After obtaining approval of the clinical trial protocol from the Ministry of Food and Drug Safety and the Institutional Review Board (IRB), any changes to the protocol that broaden

the trial procedures, increase risk, alter patient eligibility criteria, or add new safety information must be approved by the IRB and the Ministry of Food and Drug Safety. When amending the protocol, the date of revision, reason for the amendment, and details of the changes must be documented and retained.

If the changes are minor or reduce patient risk, expedited review by the IRB or approval by the IRB chairperson may suffice. Also, corrections of typographical errors, rewording for clarity, changes of monitors, or minor changes such as modifications to statistical analysis plans that do not affect trial conduct do not necessarily require formal approval.

The only case where protocol amendments may be implemented without IRB approval is when the amendment is necessary to eliminate an immediate and obvious hazard to the patient. In such cases, the investigator must notify the IRB in writing within 5 working days after implementing the amendment.

25.7 Protocol violations

Except in medically urgent situations, any deviation from the final signed protocol without prior agreement between the investigator and ViroMed Co., Ltd. is not permitted.

If a protocol deviation is significant enough to affect the decision on whether the subject should continue in the clinical trial, the investigator or monitor shall document the deviation in a Protocol Deviation Form and submit it to BiiV Healthcare. The decision on the patient's continued participation and related matters shall be confirmed with ViroMed Co., Ltd. as the sponsor.

26. Investigator's agreement to the clinical trial protocol

I have reviewed the clinical trial protocol and agree that it contains all necessary information for conducting this clinical trial.

I pledge to conduct the trial in accordance with the protocol, the ethical principles stated in the latest Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and relevant regulations to protect each subject to the fullest extent possible.

I agree to maintain confidentiality regarding the progress and results of this trial. I also agree that monitors may access source documents supporting the data recorded in the Case Report Form.

Signature of investigator	Date
Name of investigator	

Title of investigator

Name of clinical site

27. References

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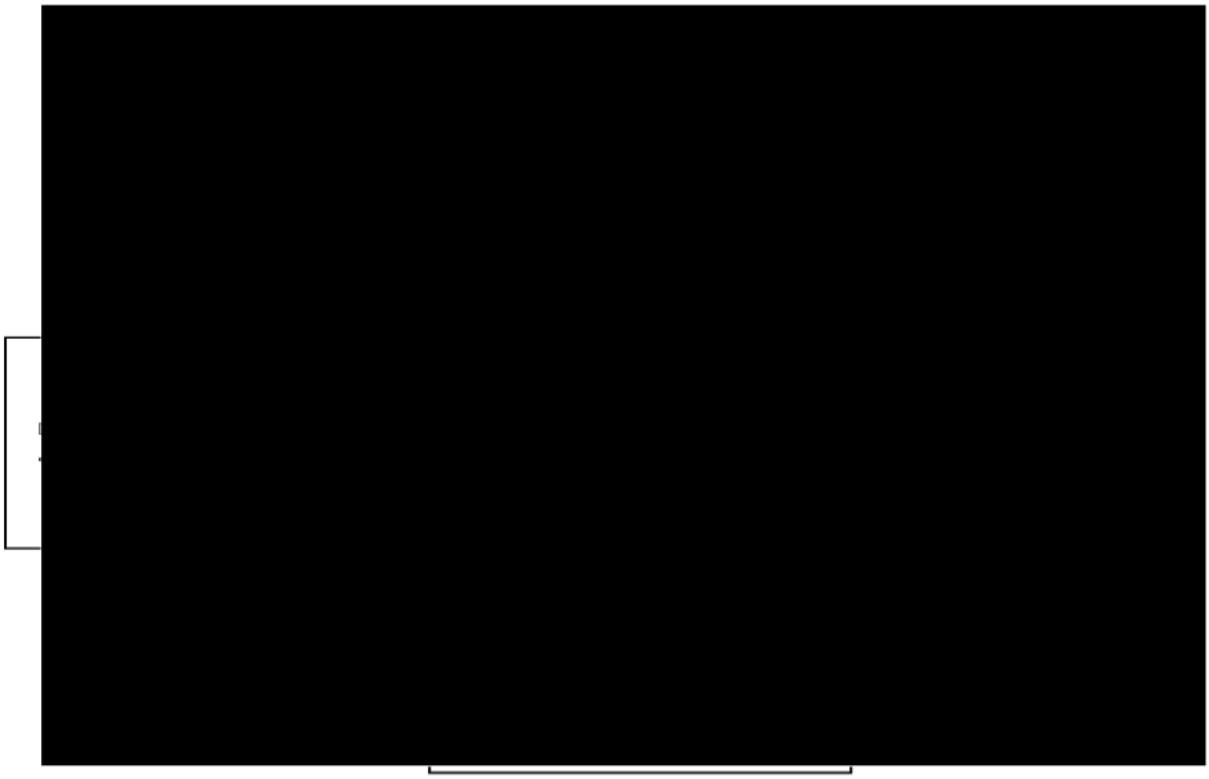
APPENDIX

[Appendix 1] Organizational chart of the clinical trial



[Appendix 2] Declaration of Helsinki

Ethical principles for medical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975, 35th World Medical Assembly, Venice, Italy, in October 1983 and

41st World Medical Assembly, Hong Kong, in September 1989.

48th General Assembly, Somerset West, Republic of South Africa October 1996 52nd World Medical Assembly, Edinburgh, Scotland, October 2000

A. Preface

1. The World Medical Association has presented ethical principles as guidelines for physicians and researchers involved in medical research using human subjects through the Declaration of Helsinki. Medical research involving human subjects includes research on identifiable human material or data.
2. Promoting and protecting human health is the duty of physicians. Physicians' knowledge and conscience must be dedicated to fulfilling this duty.
3. The World Medical Association's Declaration of Geneva urges the physician's duty by stating, "The health of my patient will be my first consideration." Additionally, international medical ethics agreements declare that "when administering treatments that may weaken the physical or mental state of subjects, physicians must act solely in the interest of the subject."
4. The advancement of medicine is ultimately partly based on experimentation involving human subjects.
5. In medical research involving human subjects, the well-being of the subject must take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve preventive, diagnostic, and therapeutic methods and to enhance understanding of the causes and processes of diseases. Even well-established preventive, diagnostic, and therapeutic methods require ongoing evaluation of their effectiveness, efficacy, usefulness, and quality.
7. Most current medical care and research involve various risks and burdens related to preventive, diagnostic, and therapeutic methods.
8. Medical research must conform to ethical standards that promote respect for all humanity and protect the health and rights of people. Since some experimental groups may be exposed to risks, special protections are necessary. Researchers must recognize the special needs of subjects who are economically or medically disadvantaged. Special caution is required for subjects who cannot give informed consent, who may have consented under duress, who derive no personal benefit from the research, or who undergo research combined with treatment.
9. Researchers conducting human subject research must be familiar with international requirements as well as the ethical and legal requirements and regulations of their own countries. However, no national ethical or legal requirements or regulations may reduce or exclude any provisions of this declaration intended to protect subjects.

B. Fundamental principles for all medical research

10. It is the physician's duty to protect the life, health, privacy, and dignity of research subjects in medical research.
11. Medical research involving human subjects must generally conform to accepted scientific principles, be based on sufficient knowledge derived from scientific literature and other relevant sources, and supported by appropriate laboratory and, where possible, animal experimentation results.
12. When conducting research that may impact the environment, appropriate caution is required, and the welfare of animals used in experimentation must be considered.
13. The planning and conduct of each experimental procedure involving human subjects must be clearly documented in a research protocol. This protocol must be submitted to a specially constituted independent research ethics committee for review, advice, guidance, and, when necessary, approval. This committee must be independent of the investigators, sponsors, or any other undue influence. The independent committee must comply with the laws and regulations of the country where the research is conducted and has the right to inspect the research process. Investigators have the duty to report to the committee all relevant information, especially any serious adverse events. They must also disclose any funding sources, sponsors, related institutions, other potential conflicts of interest, and payments to subjects.
14. The research protocol must always include a statement confirming that ethical considerations have been addressed and that the research complies with the principles outlined in this Declaration of Helsinki.
15. Biomedical research involving human subjects can only be conducted by scientifically qualified persons under the supervision of a competent clinician. Responsibility for the research lies with the qualified physician and never with the subject, even if the subject has given consent.
16. All medical research involving human subjects must be preceded by careful assessment of predictable benefits and risks or burdens to the subjects or others. Healthy volunteers should not be excluded from participation. All clinical trial protocols must be publicly accessible.
17. Physicians must only initiate research when they are confident that the risks have been appropriately assessed and can be adequately managed. If the risks are found to outweigh the potential benefits, or if definitive evidence exists indicating a positive and beneficial outcome, the trial must be stopped.
18. Medical research involving human subjects should only be conducted when the importance of the objective outweighs the risks and burdens to the subjects. This is especially important when the subjects are healthy volunteers.
19. Medical research is justifiable only when there is a reasonable likelihood that the group in which the research is conducted will benefit from the results.
20. Subjects must be volunteers and must be informed of their participation.
21. The rights of subjects to safeguard their own safety must be respected. Privacy must be protected, confidentiality of personal information assured, and all measures taken to minimize physical and mental suffering and harm to personal dignity caused by the research.
22. Subjects must be adequately informed in advance about the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, anticipated benefits, potential risks, and discomforts of the study. They must also be informed that they are free to refuse participation or to withdraw consent at any time without penalty. The physician must ensure that the subject

has understood all information and obtain freely given informed consent, preferably documented in writing. If written consent cannot be obtained, oral consent must be obtained in the presence of a witness and formally documented.

23. When obtaining consent, physicians must pay special attention to ensure that the subject is not under any undue influence or coercion and that the consent is not based on false expectations. If such conditions exist, consent must be obtained by an independent physician who has no connection with the study and who is fully informed.
24. When subjects are legally incompetent, physically or mentally incapable of giving consent, or minors, consent must be obtained from legally authorized representatives. Such groups should only be involved in research if the research is necessary to promote the health of the group and cannot be carried out on legally competent persons.
25. In cases where minors or others legally considered incapable can still express their willingness to participate, consent must be obtained both from the legally authorized representatives and from the subjects themselves.
26. Research involving subjects who cannot provide informed consent, including through proxy or prior consent, may only be conducted if the physical or mental condition that prevents consent is a necessary characteristic of the research population. The research protocol submitted for review must specify the reasons for involving such subjects and include provisions for obtaining consent from the subject or their legal representative as soon as possible.
27. Both authors and publishers have ethical responsibilities. Researchers must ensure accuracy in reporting research results. Both positive and negative results must be published or otherwise publicly available. Sources of funding, institutional affiliations, and any possible conflicts of interest must also be disclosed in publications. Research not in accordance with the principles of this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with treatment

28. Physicians may only conduct medical research combined with treatment to the extent that it is recognized by all as helpful in the prevention, diagnosis, or treatment of disease. When conducting such research, additional regulations to protect the subjects must be followed.
29. The potential benefits, risks, burdens, and effectiveness of adopting new methods must be well compared with the best current methods of prevention, diagnosis, and treatment. This applies even in cases where there are no known preventive, diagnostic, or therapeutic methods and placebos or no treatment are used.
30. At the conclusion of the study, all subjects who participated must be assured access to the best proven preventive, diagnostic, and therapeutic methods identified by the study.
31. Physicians must clearly inform subjects which parts of their treatment are related to the research. Refusal to participate in the study must not adversely affect the physician-subject relationship.
32. When known preventive, diagnostic, or therapeutic methods are unavailable or ineffective, and it is judged that the intervention may save life, improve health, or reduce suffering, physicians should be free to use unproven or new methods with the subject's informed consent. Whenever possible, these new methods should be the object of research designed to evaluate their safety and efficacy. All new

information must be recorded and, where possible, published. Other relevant guidelines set forth in this Declaration must also be followed.

[Appendix 3] Compensation policy for research subjects

Compensation policy for research subjects

ViroMed Co., Ltd. strives to minimize the burden on patients during this clinical trial in cases where treatment or hospitalization is required due to adverse reactions caused directly by gene injection, excluding cardiovascular-related adverse reactions.

1. Compensation principle

1) ViroMed Co., Ltd. compensates for physical injuries (including death) sustained by research subjects.
2) ViroMed compensates subjects if physical injury occurs and the cause of the injury is proven to be due to administration of the investigational drug used in the clinical trial.
3) Compensation is provided only for serious injuries that are persistent or disabling, not for temporary pain or symptoms that are easily treatable.
4) Compensation is given for injuries caused directly by adverse reactions to the investigational drug or injuries arising during the treatment of such adverse reactions.

2. Adverse reaction management requirements

1) Subjects must faithfully comply with the study protocol.
2) Any adverse reactions must be reported immediately to the principal investigator to prepare appropriate measures.

3. Cases where compensation will not be provided

1) ViroMed will not compensate if the cause of injury is proven not to be related to the investigational drug used in the clinical trial.
2) Compensation will not be provided for injuries caused by adverse reactions to drugs or other treatments not administered or provided under the supervision of the principal investigator or ViroMed.
3) No compensation if the clinical research fails to provide benefits such as increased myocardial perfusion or improved myocardial contractility.
4) Injuries caused by failure to comply with the mutually agreed study protocol or by the subject's failure to complete gene injection as planned in each study group will not be compensated.
5) Compensation will not be provided if the subject violates protocol compliance in ways that affect the study's validity or safety.
6) Injuries caused by the subject's negligence will not be compensated.
7) Injuries resulting from the natural progression of disease will not be compensated.

3. Compensation assessment criteria

1) The amount of compensation should be appropriate to the nature, severity, and permanence of the injury, and comparable to similar injuries generally compensated under Korean law.
2) If there is disagreement on the compensation amount between the subject and ViroMed, expert advice acceptable to both parties should be sought.

4. Relief standards

1) Gene injection is performed during standard preoperative tests commonly conducted on patients undergoing coronary artery bypass surgery, so there should be no additional hospitalization or costs incurred.
2) All expenses related to additional cardiac MRI tests during preoperative examination, postoperative follow-up cardiac MRI, and diagnosis/treatment of cardiovascular side effects caused by gene injection will be supported.
3) Efforts will be made to minimize patient burden if treatment or hospitalization is required due to non-cardiovascular adverse reactions caused by gene therapy.

ViroMed pledges to carefully consider the above points to ensure research subjects suffer no disadvantages from this trial. If any problems arise due to this trial, we commit to taking responsibility in accordance with this compensation policy for research subjects.

[Appendix 4] Informed consent form and patient consent form

Protocol No. VM202RY-VM01

Informed consent form and patient consent form

Title of clinical trial

[Open-label, non-comparative, dose-escalation, single-center, phase 1 trial to evaluate the safety of VM202RY gene medicine injected into the cardiac muscle of incompletely revascularized area after CABG in patients with ischemic heart diseases]

To the Subject,

Your participation in this clinical trial is entirely voluntary.

Please carefully read the following explanation about the clinical trial and the investigational drug. If you are willing to participate, kindly sign this informed consent document.

It is very important that you read all of the following information carefully. If you decide to participate in this study, the purpose of the research—including the potential benefits and risks you may face—is described below. If there is anything in this explanation or any terms you do not understand, please feel free to ask the study nurse, principal investigator, or research staff, and they will explain it to you.

Please note that this clinical study is being conducted solely for research purposes to obtain new scientific information.

1. Voluntary participation in the clinical trial

Your decision to participate in this clinical trial will be fully respected. If you choose not to participate, you will not be treated unfavorably or be at any disadvantage in any way.

You are being invited to participate in this clinical trial conducted by the Department of Thoracic and Cardiovascular Surgery at Seoul National University College of Medicine. However, participation in this study is entirely voluntary and not mandatory.

The choice is yours. It is very important that you fully understand the reasons for conducting the study and all related information before deciding whether or not to participate. If needed,

feel free to discuss with people close to you and make your decision after thorough understanding.

2. Purpose of the clinical trial

Ischemic heart disease is primarily caused by the narrowing (stenosis) of the coronary arteries that supply blood to the heart. Coronary artery bypass grafting (CABG) is a standard surgical procedure for ischemic heart disease, where a new route for blood flow is created using other blood vessels from the patient's body to bypass the narrowed coronary arteries and restore blood supply to the heart.

However, in patients whose coronary artery diameter is less than 1 mm, it can be technically difficult to perform vascular anastomosis due to coexisting conditions such as arterial calcification. In such cases, it becomes impossible to supply sufficient blood to the affected myocardium. Currently, treatment options for patients with these types of coronary artery territories are limited.

Gene therapy for ischemic heart disease aims to improve myocardial function by injecting genes capable of inducing angiogenesis (formation of new blood vessels) into such regions of the heart muscle, thereby increasing blood flow in the targeted area.

In this study, patients will undergo standard CABG surgery. For those in whom complete revascularization is not expected due to small vessel size or lack of usable vessels, the investigational gene (VM202RY; pCK-HGFX7), which encodes for hepatocyte growth factor (HGF), will be directly injected into the myocardium. The goal of this study is to evaluate the safety of the drug and injection method, and to determine the appropriate effective dose.

3. What is VM202RY?

VM202RY is a DNA-based gene therapy developed by ViroMed Co., Ltd. It is designed to produce two isoforms of hepatocyte growth factor (HGF) simultaneously, in a manner similar to the natural human body. Although HGF was originally identified as a substance that promotes liver cell proliferation—hence the name—it has since been found to stimulate the growth of vascular endothelial cells and is known to be elevated in ischemic conditions in most organs, helping to reduce ischemic damage.

Recent studies suggest that VM202RY not only suppresses fibrosis (scarring) in heart muscle tissue following myocardial infarction (heart attack) but also has a direct protective effect on heart muscle cells. These findings have led to the suggestion that VM202RY may represent a new treatment approach for ischemic heart disease.

4. Why you have been selected as a study subject

You have been diagnosed with coronary artery disease and are scheduled to undergo coronary artery bypass grafting (CABG). In particular, some areas of your coronary arteries are so narrow that they cannot be bypassed effectively, meaning it may not be possible to deliver sufficient blood flow to the corresponding heart muscle tissue. This condition is referred to as incomplete revascularization.

In this study, along with the standard CABG procedure, the gene (VM202RY; pCK-HGFX7) that produces hepatocyte growth factor (HGF), which promotes the formation of new blood vessels, will be directly injected into the heart muscle areas where incomplete revascularization is expected. This new approach is called “therapeutic angiogenesis.” Gene therapy, as a novel treatment method, may be beneficial for patients like you, for whom standard CABG alone may not fully address all ischemic regions.

This treatment has shown positive results in animal studies and is being tested in clinical trials in developed countries, though it is not yet an established standard therapy. Because you are likely to have areas of incomplete revascularization, you are being invited to participate in this clinical trial for therapeutic angiogenesis using gene therapy.

5. Voluntary participation

Participation in this research is entirely voluntary. Even if you choose not to participate, it will not affect your future treatment in any way.

6. Clinical trial process and procedures

If you are confirmed to be eligible and give your consent to participate, you will be enrolled in the clinical trial. After signing the informed consent form and if your vascular condition during surgery meets the trial’s criteria, the hepatocyte growth factor gene will be injected into your heart muscle.

In this study, following completion of CABG, the gene VM202RY (pCK-HGFX7) will be injected into the distal portion of vessels with incomplete revascularization. For a 0.5 mg dose group, injections will be administered at two sites on each side of the vessel, totaling four injection sites. For 1 mg or 2 mg dose groups, injections will be made at four sites on each side, totaling eight injection sites.

You will receive one of the three possible doses. However, if it is determined during surgery that vascular anastomosis is feasible—even though preoperative tests suggested otherwise—you will be excluded from the trial (screening failure) and receive standard CABG surgery instead.

7. Duration of clinical trial participation

This trial consists of two phases: the gene therapy phase and the follow-up observation phase.

- The first phase (gene therapy phase) coincides with the standard 7-day hospitalization period for coronary artery bypass grafting (CABG).
- The second phase (follow-up observation phase) includes outpatient visits and examinations at 2, 4, 8, 12, and 24 weeks after the gene injection.

The planned study duration is 24 weeks. At 3 months, you will undergo an echocardiogram, a nuclear medicine study of heart blood flow and function, and a cardiac MRI. Outpatient follow-up will continue for 6 months to monitor your clinical status.

Except for the cardiac MRI, these are standard post-operative assessments and would not be additional tests solely due to your participation in this study.

In addition, regardless of the results of this clinical trial, follow-up will be conducted at 1, 2, 3, 4, and 5 years after VM202RY administration to check for the occurrence of cancer, survival status, and any serious adverse events. These follow-ups may be conducted via outpatient visits or phone calls.

8. Number of subjects

A total of 9 patients will participate in this study, with 3 patients in each of the 3 dose groups.

If a dose-limiting toxicity (DLT) occurs during the trial, up to 18 patients may be enrolled.

9. Expected risks or discomforts

You have coronary artery disease requiring coronary artery bypass grafting. Some parts of your coronary arteries may be too narrow to allow for adequate blood flow, raising the possibility of incomplete revascularization. In this study, VM202RY will be injected into such areas to stimulate the formation of new blood vessels. As such, it is important for you to understand the possible risks associated with both the bypass surgery and the gene therapy.

① While you will receive the most appropriate treatment based on your condition, the general risks associated with CABG always remain. These include:

- The need for repeat surgery due to post-operative bleeding
- Heart failure requiring cardiopulmonary bypass or resuscitation
- Death

These risks are not unique to this trial but are inherent in any surgery for ischemic heart disease. Such general side effects or complications are possible in any patient undergoing CABG.

② The investigational product, VM202RY, is a plasmid DNA-based gene therapy. Globally, around 190 clinical trials have been conducted using plasmid DNA, and no serious adverse events have been reported. However, since this specific plasmid DNA has not been used in other trials before, there may be unpredictable risks. Theoretical risks of gene therapy include:

- Bleeding or damage at the injection site
- Resulting arrhythmia, myocardial infarction, or worsening heart failure

However, animal studies with VM202RY have shown minimal tissue damage at the injection site and no significant toxicity.

Because HGF promotes blood vessel formation, there is a theoretical risk it might stimulate the growth of microtumors (very small, undetectable tumors). Nevertheless, preclinical studies suggest that HGF gene therapy in plasmid DNA form does not promote tumor growth.

HGF may also theoretically worsen diabetic retinopathy.

Therefore, you will be screened for proliferative retinopathy, and if signs are detected, you will be excluded from this study.

Based on preclinical animal data, it is expected that you will receive this gene therapy without significant complications. However, like any new treatment, unforeseen side effects may occur, and long-term safety data are not yet fully established.

If any new information arises that may affect your willingness to continue participation in the study, you or your legal representative will be informed immediately.

10. Alternative treatments

You are not obligated to participate in this clinical trial for gene therapy in ischemic heart disease. Treatments such as coronary artery bypass grafting (CABG) are commonly offered for patients with your condition. However, in your case, certain surgical target areas may involve calcified vessels, diffuse atherosclerotic disease, or small vessels with diameters less than 1 mm, making bypass grafting impossible.

As a result, incomplete revascularization is expected in some regions of your heart. You are being considered for this gene therapy study because of this situation. Outside of the study, the standard treatment available to you would be CABG only to areas where revascularization is feasible, excluding regions with anticipated incomplete perfusion.

11. Examinations to be performed

You will undergo tests to:

- Confirm the state of your condition, and
- Determine whether you are responding to gene therapy and/or CABG.

The specific test schedule and clinical visit details will be explained in a separate document (study flow chart).

12. Expected benefits

Gene therapy for ischemic cardiovascular disease is a novel therapeutic approach. In this study, gene therapy using VM202RY is administered as an adjunct treatment—after CABG has been performed to the best possible extent—to regions with incomplete revascularization.

While VM202RY has shown positive results in animal models by promoting revascularization and preventing myocardial fibrosis, its effectiveness in humans has not yet been proven, and therapeutic benefits cannot be guaranteed.

During the clinical trial, your symptoms and clinical signs will be closely monitored. Follow-up testing such as echocardiography, myocardial SPECT, and cardiac MRI will be conducted to evaluate the safety and effectiveness of the gene therapy.

13. Prohibited medications

There are no strict restrictions on other treatments during the study. However, you are advised to consult the research team before starting any new treatment, for your safety and well-being.

14. Costs and compensation for participation

Typically, patients undergoing CABG attend outpatient visits every 1–3 months, depending on their condition. Participants in this study will follow the same schedule, so no additional clinic visits are required because of your participation.

However, gene therapy is a novel treatment not currently covered by health insurance, and some associated tests are also not reimbursed by insurance.

The study sponsor will cover the costs of procedures not routinely required for standard CABG patients, including:

- Pre- and post-operative cardiac MRI
- Echocardiography
- Myocardial SPECT
- Fundus (retinal) examinations, and
- Other tests necessary for the clinical trial.

Additionally, participants will receive a transportation stipend of 50,000 KRW per visit to compensate for travel expenses. Therefore, you will not incur any additional financial burden by participating in this clinical trial.

No other compensation or financial benefit will be provided.

In the event of unexpected adverse reactions caused by the intramyocardial injection of VM202RY requiring further treatment, support will be provided, in accordance with the subject compensation policy (attached separately).

15. Compensation for study-related injuries

If you experience any injury as a result of participating in this study and receiving the investigational drug, you will be compensated in accordance with the Subject Compensation Policy. If any injury or adverse reaction related to the study occurs, you must immediately contact the principal investigator or study staff.

16. Withdrawal from the study

Even if you agree to participate in this clinical trial, you are free to withdraw your consent at any time without hesitation. Participation is completely voluntary, and you may discontinue your involvement in the study at any time, even during the trial period.

Additionally, the study may be terminated early due to administrative reasons or changes in your medical condition or treatment. In such cases, the study staff will provide you with a full explanation

17. Confidentiality

Except for you, your attending physician, and study personnel, no one will be informed of your participation in this study or the progress of your treatment.

Your medical records will not be transferred unless confidentiality is maintained. However, your records may be reviewed by regulatory authorities to oversee the proper conduct of the study. Authorized monitors or regulatory authorities, as well as representatives designated by ViroMed Co., Ltd. (the sponsor), may access your hospital records for study-related purposes.

If you consent, your participation in this study may be disclosed to other physicians involved in your care. Your records will be kept for 10 years in accordance with the law and will be destroyed afterward.

18. Investigator contact

If you have any questions regarding this study, please contact the following number:

Investigator:	Ki-bong Kim	02-2072-3482
Clinical research coordinator:	Hyo-sook Lee	010-2012-9452

Schedule of evaluations and vistis

Procedure	Screening	Treatment					Follow-up				
Visit schedule	-21 ~ -1 day	Day 0	Day 1	Day 2	Day 5	Day 7	Week 2 (±4D)	Week 4 (±4D)	Week 8 (±7D)	Week 12 (±7D)	Week 24 (±7D)
Informed consent	X										
Inclusion / Exclusion criteria	X	X									
CABG+intramyocardial injection		X									
Physical exam	X	X					X	X	X	X	X
Clinical symptoms and adverse reactions		X	X	X	X	X	X	X	X	X	X
Basic information on subject	X										
Medical history	X										
Hematology	X	X	X	X	X	X	X	X		X	X
Biochemistry	X		X	X	X	X	X	X		X	X
Urinalysis	X		X	X	X	X	X	X		X	X
Urine pregnancy test	X										
ESR / CRP	X		X			X	X	X		X	X
CK, CK-MB, LDH, Troponin I	X	X	X	X	X	X	X	X		X	X
Serology	X										
PT, aPTT, Fibrinogen	X										
Anti-HGF antibody	X						X	X			X
Serum HGF protein	X					X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X	X	X	X	X	X	X	X		X	X
Holter monitoring	X					X	X	X		X	X
Cancer marker test / fecal occult blood test	X									X	X
Fundoscopy	X						X	X		X	X
MIBI SPECT	X									X	X
MRI	X									X	X
TTE	X					X				X	X
CAG	X										X
Concurrent medication	X	X	X	X	X	X	X	X	X	X	X

* Day 0: testing and blood sampling on day 0 of surgery are performed prior to surgery. If the screening test results are available within 24 hours of surgery, the day 0 test may be omitted and replaced with the screening results.
- Treatment (7 days): subjects are hospitalized and treated.
- Long-term follow-up observations are conducted 1, 2, 3, 4, and 5 years after VM202RY administration to confirm the subject's survival and occurrence of cancer.

Protocol No. VM202RY-VM01

Consent Form

Name of subject: Screening number: S

Study title: Open-label, non-comparative, dose-escalation, single-center, phase 1 trial to evaluate the safety of VM202RY gene medicine injected into the cardiac muscle of incompletely revascularized area after CABG in patients with ischemic heart diseases

1. I have been informed about the method, expected effects and side effects, and the availability of alternative treatments regarding the hepatocyte growth factor gene therapy through the provided information sheet. I fully understand the explanation and give my consent to undergo the procedure.
2. I understand that I may choose to withdraw from participation in the study at any time without any consequences.

Accordingly, I agree to follow the instructions given during the clinical trial period, to cooperate faithfully with the principal investigator or study staff, and to immediately notify them if there are any changes in my health or if any unexpected symptoms occur. By signing below, I voluntarily agree to participate in this clinical trial.

Subject Name: _____

Date: _____ Signature: _____

Legal representative Name: _____

Date: _____ Signature: _____

I, the undersigned investigator, confirm that I have fully explained the overview of this clinical trial, the efficacy and safety of the investigational drug, and the possible side effects of the drug to the patient and/or their guardian.

Investigator Name: _____

Date: _____ Signature: _____

Informed consent form for Gene Therapy

Subject	Name:
	Birth date:
Informed consent counselor	Name:
	Birth date:
Date	

1. Purpose of gene therapy

Ischemic heart disease is primarily caused by the narrowing of the coronary arteries that supply blood to the heart. Coronary artery bypass grafting (CABG) is a standard surgical treatment for ischemic heart disease that creates a new route for blood flow to the heart by bypassing the narrowed coronary arteries using other blood vessels from the body. However, when the inner diameter of the patient's own coronary arteries is less than 1 mm, technical difficulties such as vascular calcification may make vascular anastomosis impossible, resulting in insufficient blood supply to the myocardium. Therefore, treatment options for patients with such coronary artery regions are currently limited. Gene therapy for ischemic heart disease aims to improve myocardial function by administering genes known to promote angiogenesis in the affected myocardial area, thereby generating new blood vessels and increasing blood flow at the injection site. In this study, after performing the standard CABG surgery, gene therapy will be administered to patients expected to have incomplete revascularization due to very small vessels or insufficient available vessels. During surgery, the gene encoding hepatocyte growth factor (HGF), which promotes blood vessel growth (VM202RY; pCK-HGFX7), will be directly injected into the myocardium of the affected area to verify the safety of this drug and its method of administration.

2. Expected therapeutic outcomes of gene therapy

VM202RY is a DNA-based gene therapy developed by ViroMed Co., Ltd., which simultaneously produces two forms of hepatocyte growth factor similar to those naturally present in the human body. The hepatocyte growth factor gene was initially identified as a substance that promotes liver cell division and named accordingly; however, subsequent research has shown that it promotes the growth of vascular endothelial cells and that its concentration increases in ischemic conditions in most organs, where it acts to suppress ischemic cell damage. Recent studies indicate that VM202RY not only inhibits fibrosis occurring in the heart muscle after myocardial infarction but also provides direct protective effects to cardiomyocytes, making it a promising new treatment for ischemic heart disease.

You require coronary artery bypass grafting (CABG) due to coronary artery disease. However, in some coronary artery regions, your own coronary arteries are so narrow that bypass surgery is technically impossible, making it difficult to supply sufficient blood to the myocardial cells in those areas. This may result in incomplete revascularization. In this study, in addition to the standard treatment of CABG, you will be administered a gene (VM202RY; pCK-HGFX7) that produces hepatocyte growth factor (HGF), which promotes the formation of new blood vessels in the areas of incomplete revascularization. This new treatment is called "angiogenesis therapy."

This novel gene therapy may be beneficial in cases like yours, where the standard CABG treatment alone is unlikely to fully treat all ischemic areas. Although animal studies have shown positive therapeutic results and clinical trials are being conducted in developed countries, this treatment is not yet a complete cure.

If successful, this therapy could induce new blood vessel formation in the incompletely revascularized myocardial areas through the expression of HGF protein. This would deliver nutrients to the ischemic myocardium, prevent ongoing damage to myocardial cells caused by disrupted blood flow, and inhibit the progression of myocardial fibrosis resulting from myocardial infarction. Consequently, it is expected to help restore cardiac function, such as improving contractility in previously nonfunctional myocardium. However, even if treatment of the incompletely revascularized myocardial area is achieved, full recovery of normal heart function cannot be guaranteed.

Current research indicates that incomplete revascularization reduces early and mid-term survival rates in patients aged 75 or younger.

1. Expected adverse events of gene therapy

You require coronary artery bypass grafting (CABG) due to coronary artery disease. In particular, some coronary artery regions have vessels so narrow that bypass surgery is not possible, which may result in incomplete revascularization and insufficient blood supply to the myocardial cells in those areas. In this study, in addition to the standard treatment of CABG, you will receive VM202RY, a gene therapy that promotes the formation of new blood vessels in the areas of incomplete revascularization. Therefore, you should understand the possible side effects associated with both CABG and gene therapy.

① You will receive the most appropriate treatment for your condition; however, the risks associated with general CABG surgery always exist. These risks include reoperation due to postoperative bleeding, cardiopulmonary bypass or cardiopulmonary resuscitation due to postoperative heart failure, and death. Such surgical risks related to ischemic heart disease cannot be avoided even in a clinical trial setting. These common side effects or complications can occur in all patients with angina.

② VM202RY used in this trial is in the form of plasmid DNA. Globally, over 190 clinical trials using plasmid DNA-based gene therapies have been conducted, and no serious adverse effects have been reported related to these. However, since the plasmid DNA used in this study has not been used in previous clinical trials, unpredictable side effects may occur at this time. Theoretical possible side effects of gene therapy include bleeding and injury at the injection site, which could cause arrhythmia, myocardial infarction, or worsening of heart failure. However, animal studies using VM202RY have shown that injection site injury is very limited, and no serious toxicity was observed. Since HGF promotes angiogenesis, there is a theoretical possibility that it could stimulate the growth of very small tumors that are currently too small to be detected. However, animal studies have shown that administration of HGF gene in the form of plasmid DNA does not induce tumor growth. Theoretically, HGF could worsen diabetic retinopathy. Before receiving this gene therapy, you will undergo an eye examination to check for proliferative retinopathy. If there is evidence that you have proliferative retinal disease, you will be excluded from this study. According to preclinical animal studies, it is expected that you will receive this gene therapy without significant complications; however, like other advanced treatments, unforeseen side effects may occur, and there is currently no detailed data on the long-term safety of this gene therapy

② If any new information arises that may affect the subject's willingness to continue participating in the clinical trial, the subject or their guardian will be informed immediately.

For each of the following items, please place a checkmark (√) in the box ☐ once you have received an explanation from the counselor and fully understood the content.

1) Gene therapy is legally prohibited for sperm, eggs, embryos, or fetuses ☐
2) I have received an explanation from the gene therapy institution regarding the necessary measures to ensure the safety of gene therapy. ☐
3) Even if the consenting person agrees to the above matters, consent can be withdrawn at any time before the treatment begins. ☐
4) The gene therapy institution is obligated to take necessary measures to protect the personal information of the consenting person. ☐

I hereby declare that my consent to the above matters is given voluntarily

Signature

Subject : _____

Informed consent counselor : _____

[Appendix 5] WHO toxicity scale

WHO recommendations for grading of acute and subacute toxic effects

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
1. Hematologic (adults)					
Hemoglobin g/100 mL	≥ 11.0	9.5 - 10.9	8.0 – 9.4	6.5 – 7.9	< 6.5
Leukocyte 1000/cmm	≥ 4.0	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	< 1.0
Granulocyte 1000/cmm	≥ 2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
Platelets 1000/cmm	≥ 100	75 – 99	50 – 74	25 – 49	< 25
Hemorrhage	None	Petechiae	Mild blood loss	Gross blood loss	Debilitating blood loss
2. Gastrointestinal					
Bilirubin	≤ 1.25 x N*	1.26 – 2.5 x N	2.6 – 5 x N	5.1 – 10 x N	> 10 x N
SGOT/SGPT	≤ 1.25 x N	1.26 – 2.5 x N	2.6 – 5 x N	5.1 – 10 x N	> 10 x N
Alkaline phosphatase	≤ 1.25 x N	1.26 – 2.5 x N	2.6 – 5 x N	5.1 – 10 x N	> 10 x N
Oral	No change	Soreness/erythema	Erythema, ulcers; can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
Nausea/vomiting	None	Nausea	Transient	Vomiting requiring extra therapy	Intractable vomiting
Diarrhea	None	Transient < 2 days	Tolerable but > 2 days	Intolerable requiring therapy	Hemorrhagic dehydration
3. Renal, bladder					
BUN or blood urea	≤ 1.25 x N	1.26 – 2.5 x N	2.6 – 5 x N	5.1 – 10 x N	> 10 x N
Blood creatinine	≤ 1.25 x N	1.26 – 2.5 x N	2.6 – 5 x N	5.1 – 10 x N	> 10 x N
Proteinuria	None	1+, < 0.3g/100mL	2-3+, 0.3-1.0g/mL	4+, > 1.0g/100mL	Nephrotic syndrome
Hematuria	None	Microscopic	Gross	Gross + clots	Obstructive uropathy
4. Pulmonary	None	Mild symptoms	Exertional dyspnea	Dyspnea at rest	Complete bed rest required
5. Fever-drug	None	Fever < 38℃	Fever 38℃ - 40℃	Fever > 40℃	Fever with hypotension
6. Allergic	None	Edema	Bronchospasm; no parenteral therapy needed	Brochospasm; parenteral therapy needed	Anaphylaxis
7. Cutaneous	None	Erythema	Dry, desquamation, vesiculation, pruritus	Mist, desquamation, ulceration	Exfoliative dermatitis; necrosis requiring, surgical intervention

8. Hair	None	Minimal hair loss	Moderate, patchy alopecia	Complete alopecia but reversible	Nonreversible alopecia
9. Infection (specify site)	None	Minor infection	Moderate infection	Major infection	Major infection with hypotension
10. Cardiac					
Rhythm	No change	Sinus tachycardia > 110 at rest	Unifocal PVC, arterial arrhythmia	Multifocal PVC	Ventricular tachycardia
Function	No change	Asymptomatic but abnormal cardiac sign	Transient symptomatic dysfunction; no therapy required	Symptomatic dysfunction responsive to therapy	Symptomatic dysfunction nonresponsive to therapy
Pericarditis	No change	Asymptomatic effusion	Symptomatic; no tap required	Tamponade; tap required	Tamponade; surgery required
11. Neurologic					
State of consciousness	Alter	Transient lethargy	Somnolent < 50% of waking hours	Somnolent > 50% of waking hours	Coma
Peripheral	None	Paresthesias and/or decreased tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or marked motor loss	Paralysis
Constipation**	None	Mild	Moderate	Abdominal distention	Distention and vomiting
12. Pain* **	None	Mild	Moderate	Severe	Intractable

These guidelines resulted from two international meetings organized on the initiative of the World Health Organization, as published by Miller AB, et al: Cancer 1981; 47: 207

*N, upper limit of normal

** Constipation does not include constipation resulting from narcotics.

*** Only treatment-related pain is considered, not disease-related pain. The use of narcotics may be helpful in grading pain, depending upon the tolerance level of the patient.

[Appendix 6] JNC VII Guide to Prevention and Treatment of Hypertension

Recommendations

Classification and management of blood pressure for adults aged 18 years or older

BP classification	Systolic BP* (mmHg)	Diastolic BP* (mmHg)	Lifestyle modification	Initial drug therapy	
				Without compelling indications	With compelling indications
Normal	Less than 120	Less than 80	Encourage	No antihypertensive drug indicated	Drug(s) for compelling indications. ‡
Prehypertension	120 – 139	80 – 89	Yes		
Stage 1 hypertension	140 – 159	90 – 99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications. ‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCD) as needed.
Stage 2 hypertension	160 and above	100 and above	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

Drug abbreviations: ACEI-angiotensin converting enzyme inhibitor;ARB-angiotensin receptor blocker;BB-beta blocker;CCB-calcium channel blocker.

* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

[Appendix 7] Killip class

Class	Definition
Killip class I	individuals with no clinical signs of heart failure
Killip class II	individuals with rales in the lungs, an S3 gallop, and elevated jugular venous pressure*
Killip class III	individuals with frank pulmonary edema.
Killip class IV	individuals in cardiogenic shock

* Reference: Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med. 2001 Aug 23;345(8):574-81

[Appendix 8] Canadian cardiovascular society (CCS) class

Canadian cardiovascular society functional classification of angina pectoris

Class	Definition
Class I	Ordinary physical activity (eg. Walking and climbing stairs) dose not cause angina; angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening; when walking>2 blocks on level ground; or when climbing more than 1 flight of stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity; angina occurs on walking 1 to 2 blocks on level ground or climbing 1 flight of stairs at a normal pace in normal conditions.
Class IV	Inability to perform any physical activity without discomfort; anginal symptom may be present at rest

Adapted from Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class; adventages of new specific activity scale Circulation. 1981;64;1227~1234.

[Appendix 9] New York heart association (NYHA) functional classification

A functional and therapeutic classification for prescription of physical activity for cardiac patients.

Class	Definition
Class I	Patients with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity dose not cause undue fatigue, palpitation, dyspnea, or anginal pain..
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity cause fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.