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### Citation

Poorter, J. de. (2010, January 28). *Gene therapy and cement injection for the treatment of hip prosthesis loosening in elderly patients*. Retrieved from <https://hdl.handle.net/1887/14642>

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**Note:** To cite this publication please use the final published version (if applicable).

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## Gene Therapy in aseptic prosthetic replacement loosening. Clinical protocol A phase 1 study

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## Scheme

### *Entry criteria*

Elderly patients with debilitating pain from aseptic loosening of the hip prosthesis, as proven with arthrography, who are ineligible for surgery due to significant comorbidity

### *Registration*

History, physical examination, radiological studies, laboratory data.

### *Treatment plan*

Hospital admittance for 11 days. Intra-articular HAdV-5 vector injection on day 1, followed by intra-articular prodrug injection on day 3. Periprosthetic bone cement injection 4-7 days after prodrug injection under local anaesthesia (spinal). Mobilisation and discharge one day after cement injection.

### *Dose escalation*

The first three patients will be injected with  $3 \times 10^9$  HAdV-5 vector particles. Dose escalation will proceed to  $1 \times 10^{10}$ ,  $3 \times 10^{10}$ , and  $1 \times 10^{11}$  HAdV-5 vector particles for three patients per dose group or until dose limiting toxicity occurs.

### *Evaluation*

Laboratory toxicity evaluation during first six weeks follow up. Clinical evaluation (Harris Hip Score and VAS) at 3 and 6 weeks follow up, 3 and 6 months and every year. X-rays one day after cement injection, at 6 weeks and 6 months follow up and every year. Collection of excreta for analysis of shedding from 24 h after vector-injection until negative results.

### *Duration*

One period of hospital admittance of 11 days with one single injection of vector and prodrug. Follow-up period of 5 years.

## Introduction

In the Netherlands about 20,000 total hip prostheses operations are performed annually. In the minority of total hip replacements, loosening of the femoral stem and acetabulum occurs within 10 years due to aseptic loosening.<sup>24,56</sup> Wear particles, which are released from the polyethylene acetabular component, travel to all sites accessible for joint fluid (including periprosthetic spaces) and are phagocytosed by macrophages. This causes an aseptic inflammatory reaction with stimulation of osteoclast activity. Activation of osteoclasts in turn causes periprosthetic osteolysis and loosening of the implant. Apart from this direct effect mediators released by macrophages stimulate fibroblast-like cells to invade and destroy the bone covering the joint prosthesis. The inflammatory process takes place in interface tissue, which is located periprosthetically. Interface tissue from patients with loosened prostheses exhibits similar behavior as synovial tissue from rheumatoid arthritic joints. When prosthesis loosening occurs, patients will experience more pain and walking difficulty and have a higher risk for dislocations and pathological fractures.<sup>54</sup>

After 10 years of follow-up 7-13% of patients need revision of their prosthesis due to loosening of the implant.<sup>79,112</sup> Revision surgery has a high morbidity rate especially in elderly patients with co-morbidity. In a study by Strehle *et al.*<sup>114</sup> post-operative mortality (during hospital stay) in elderly patients was 5.7%. Especially patients in ASA 3 (grading of mortality risk according to American Society of Anesthesiologists)<sup>121</sup> with cardiac insufficiency had major complications such as myocardial failure or coronary artery disease. In some patients revision-surgery is not an option at all, because benefits don't balance the tremendously high mortality risk.

In order to minimise morbidity due to revision surgery we searched for alternative treatments. In knees (and in a few hips) radiotherapy has been investigated as a means to kill synovial tissue in rheumatoid arthritis. In these studies yttrium 90 is injected into the joint to destroy the synovial tissue. Yttrium 90 was chosen as the best agent for this therapy, because it is a  $\beta$ -emitting radionucleotide (good tissue penetration, but not too extensive) with a relatively large particle size (prevents leaking out of the joint) and a short half-life (reduces radiation exposure to non-target tissues).<sup>25</sup> The results of the studies with yttrium, and other radionucleotides, are diverse. However, in a meta-analysis of randomised controlled trials, no clear evidence of the efficacy of yttrium synovectomy is shown.<sup>59</sup>

Gene therapy is a tool for delivering individual proteins to specific tissues and cells. With gene therapy, target cells can be identified, and then a gene can be delivered to these target cells to produce a corrective or killing protein.<sup>52</sup> Human Adenovirus 5 is a virus that infects cells from interface tissue with a high efficiency.

Moreover, the virus has a high particle size which, in combination with the relatively closed joint space, prevents most of it from diffusing into other tissues. When using human adenovirus 5 as a vector to express the gene *Escherichia coli nitroreductase* (Ntr), infected cells become extremely sensitive to the prodrug CB1954. The activated prodrug causes death of the infected cells.<sup>34</sup> In a study by Goossens *et al.*<sup>46</sup> it was demonstrated that genes can be transferred to synovial tissue *in vivo* in rhesus monkeys, by direct injection into the joint, and that the synoviocytes can be killed with injection of a specific prodrug. In our laboratory previous experiments have shown the efficacy of the infection and destroying of synoviocytes and fibroblasts from interface tissue by HAdV-5-Ntr (CTL102) and CB1954.<sup>30</sup> This study aims to destroy the interface tissue (which causes the loosening), by sensitising the cells to the prodrug CB1954, by means of HAdV-5-Ntr (CTL102). Successful destruction and removal of the interface tissue is expected to create a periprosthetic space accessible to the injection of bone cement. To stabilise the prosthesis and re-anchor it to the bone, bone cement is injected in the periprosthetic space. This method for stabilising loosened femoral stems and acetabula could be especially valuable in patients with high risk for complications due to surgical intervention, who are thus defined inoperable. Patients are admitted to the hospital for 11 days and there is no need for rehabilitation afterwards. This is intended to increase the mobility of the patient and decrease pain, without the risk of surgical complications.

## Objectives

### Primary endpoint

To assess the safety of intra-articular injection of the HAdV-5 vector CTL102 and the prodrug CB1954 and the percutaneous peri-prosthetic injection of bone cement.

### Secondary endpoints

- To histologically investigate a biopsy of interface tissue after the procedure to make an assessment of the alterations induced by the intervention.
- To establish that this procedure does not cause shedding of the recombinant virus into the environment.
- To investigate the possibility to stabilise the loosened prosthesis by means of bone cement.
- To investigate clinical results, i.e. pain relief and improvement in ADL

## Subjects

### Inclusion criteria

- aseptic loosened femoral stem implant, as proved by arthrography
- debilitating pain causing ADL dependency
- arthrography volume  $\leq 45$  ml, but injection of a volume of  $\leq 30$  ml will give sufficient exposure of the interface tissue to the contrast medium
- significant co-morbidity (ASA 2 and more) causing high mortality risks ( $>2.5\%$ ) during or after surgery
- ability to give informed consent and express a willingness to meet all the expected requirements of the protocol
- patients must meet the following baseline laboratory value guidelines at the screening and on day 0
  - a Haemoglobin  $> 6$  mmol/l
  - b Leukocytes  $4.0 - 20.0 \times 10^9/l$
  - c Platelets  $> 100 \times 10^9/l$
  - d AST  $< 50$  U/l
  - e ALT  $< 56$  U/l
  - f AF  $< 150$  U/l
  - g Bilirubin  $< 21 \mu\text{mol/l}$
  - h Creatinin  $< 166$  mmol/l
  - l PT  $< 14$  sec

### Exclusion criteria

- patients who fail to meet the inclusion criteria
- infection of endoprosthesis
- patients with obvious adenoviral infection (eye, nose/throat)
- patients with a history of hepatitis A, B or C or HIV infection
- patients with a history of alcohol or drug abuse
- previous gene therapy of any kind
- patients who underwent chemotherapy, radiotherapy or immune therapy in the previous 28 days
- patients with known immunodeficiency
- patients with known allergy to *E coli* proteins
- patients with life expectancy of  $<6$  months
- non-cooperating patients
- patients not able to read and understand Dutch language

## Ethical considerations

### Regulatory statement

The study will be conducted according to the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice and Hong Kong, Somerset West and Edinburgh), and in accordance with the Guidelines for Good Clinical Practice (CPMP/ICH/135/95-17<sup>th</sup> July 1996). The trial will be conducted in compliance with the protocol.

### Recruitment and consent

The protocol of this study and any subsequent amendments will be submitted to the Medical Ethics Committee (CME) of Leiden University Medical Centre and the CCMO (Central Committee on Research Involving Human Subjects). The study will not commence before formal approval has been granted.

Patients will be recruited from the outpatients' clinic of the department of Orthopedic Surgery in Leiden. Patients who meet inclusion and exclusion criteria will be informed that they are a potential study candidate, by their own orthopaedic surgeon. They will be referred to the researcher, who will inform the patient about the study. Information will be given both orally and written. The researcher will answer any questions the patient may have about the study at that time or later, and offer the patient the opportunity to participate in the study. She will also be responsible for obtaining informed consent from the patient. Patients will be given as much time as they wish to decide on participation in the study. At least 1 week should pass between the supplying of information and a positive decision to participate in the study. After approval by the subjects, their general practitioners will be notified. Although the subjects will be told they are free to leave the study at any time, it will be attempted to recruit subjects who are likely to continue the study to completion.

### Justification for the burden of the patients

A loosened prosthesis needs to be stabilised to regain function and decrease pain. The current treatment to stabilise the prosthesis is a revision arthroplasty in which the loosened prosthesis is removed and a new one is placed. Patients who undergo revision surgery will have spinal anaesthesia (or general anaesthesia). The mean surgery time for revision THA (total hip arthroplasty) is two to four hours. During surgery 1-2 litres of blood may be lost, after surgery drainage systems will collect an additional 500-1000 ml. Complications like cardiopulmonary problems may occur during or after surgery. One major risk after revision surgery is the likelihood for deep prosthetic infection (3-5%), which will

indicate removal of the prosthesis. Rehabilitation will take about 2-3 months. Patients accept this burden as a price they pay for better function of the hip and less pain.

In this study, patients with a loosened prosthesis, who cannot be operated upon, are included in the study. Currently, no treatment is available for these patients. Therefore patients included are not restrained from adequate therapy.

To adequately refix the prosthesis the interface tissue (which is responsible for the loosening) should be removed. In revision surgery this is performed manually. *In vitro* studies in our laboratory have shown that interface tissue can be killed by CTL102/CB1954 administration. To optimise local dose concentration and minimise systemic effects, CTL102 and CB1954 need to be administered as locally as possible. Intra-articular injection is an adequate method for local administration of fluids and is well tolerated. To assure free access of fluids to the periprosthetic space only patients are included with an arthrogram that shows contrast medium around the prosthesis. Therefore patients need to undergo three arthrographies (one to assure access of contrast medium, one to inject the viral vector, and one to inject the CB1954 prodrug).

When the interface tissue is successfully diminished the prosthesis needs to be refixed. To re-anchor the prosthesis to the bone, cement is injected in the periprosthetic space.

Although the primary objective of the study is to assess toxicity of local administration of CTL102/CB1954, it would be unethical to deny a patient a potentially effective therapy. For the injection of the cement, holes have to be made through the bone into the periprosthetic space. As the bone biopsies are rather painful and the bone could not be anaesthetised locally, the patients undergo spinal anaesthesia, with small risk of side effects.

To assure safety for the environment, patients will be isolated until viral shedding by the patient is excluded. Therefore patient's excreta (nose and throat swabs, urine, and faeces) are collected and analysed until negative results are obtained. Then isolation is discontinued.

To investigate safety for the patient, history, physical examination and laboratory parameter measurements are done. These examinations are necessary to detect and treat side effects as soon as possible.

### **Compensation for injury**

The chance of injury as a result of the study is small. However the LUMC has insured this risk by taking liability insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Temporary Measure regarding Compulsory Insurance for Clinical Research in Humans of 5<sup>th</sup> July 1999).



This insurance provides cover for damage to research subjects through injury or death caused by the study. Conditions for benefit of insurance amounts are noted in the WMO-declaration.

## Trial medication and investigational products

### Name and description of investigational products

- The proposed treatment involves intra-articular injection of a replication deficient adenoviral delivery vector (CTL102), engineered to deliver the gene for the enzyme *E. coli nitroreductase* (Ntr). Cells infected with the vector will synthesise the enzyme under control of the CMV promoter. The drug product CTL102 is supplied by ML Laboratories plc as a sterile, clear, colourless, isotonic aqueous solution at a nominal mean potency of between  $5 \times 10^8$  and  $1 \times 10^{12}$  particles per ml, buffered to pH 7.4, in single use polypropylene vials. CTL102 is manufactured by Cobra Bio-manufacturing plc, Keele, UK, ST5 5SP and formulated into the finished dosage form by Q-One Biotech Ltd., Glasgow, G20 0XA.
- The drug product CB1954 is supplied by ML Laboratories plc as a sterile solution of CB1954 17.8 mg/ml in solvent (N-methyl-pyrrolidone 22.2% v/v, polyethylene glycol 300 77.8% v/v). Just prior to use this prodrug in solvent is diluted using sterile saline to a maximum final concentration of 2 mg/ml.
- To stabilise the prosthesis low viscosity PMMA bone cement is used.
- For arthrography iodide contrast medium is used.
- Ethylene diamine tetra-acetate (EDTA; Sigma Chemical, St Louis, MO, USA) is used in a concentration of 2mM in a saline solution to rinse the joint before injection with the vector and prodrug.

### Summary of findings from non-clinical studies

#### *Pharmacological characteristics*

Genetic material delivered by adenovirus is not integrated in the genome of the target cells, because neither wild type nor recombinant adenoviruses are capable of integrating their genomes into infected host cells. The CTL102 virus genome remains extra chromosomal and does not replicate in the transduced cells. In all cell-lines and animals tested, CTL102 has the same tropism and infectivity as the wild type HAdV-5 from which it is derived. The primary effect of CTL102 infection of a cell will be the delivery of the Ntr gene expression cassette. After cell entry and unpackaging from the viral capsid, the CTL102 genome will exist as an extra chromosomal DNA element from

which the machinery of the infected cell will transcribe Ntr mRNA. This in turn will be translated into active nitroreductase, which will accumulate in the cytosol. Expression of the Ntr and its persistence is transient both in animal models and cell lines *in vitro*. This is presumed to be due to a combination of protein turnover within the cell, the spontaneous loss of CTL102 DNA in infected cells and cell turnover within the population.

Intracellular Ntr activity is responsible for the activation of prodrug CB1954 to a toxic bifunctional alkylating agent inside the cell. Cells able to bioactivate CB1954 are cytotoxically affected by crosslink formation at very high frequency. As a consequence, cells activating CB1954 are destroyed by death.

The intended outcome of this study is that infected cells expressing Ntr, which take up CB1954, will be killed by the activated prodrug.

The potential utility of the GDEPT (Gene-directed enzyme prodrug therapy) approach is augmented by the so-called "bystander-effect" in which neighbouring untransduced interface cells are killed during the prodrug therapy.<sup>127</sup> The Ntr/CB1954 system offers high selectivity because no natural human enzyme can activate the prodrug sufficiently to cause significant biological activity to kill cells *in vivo*.

#### *Summary of animal experiments*

In mice the peak expression level of Ntr is achieved 48 h after injection of CTL102. Continued expression ensures adequate levels of the enzyme for prodrug activation over several days. In intravenous administration of CTL102 in mice adenovirus DNA is not seen in germ cells. In the clinic CTL102 will be administered intra-articularly with low risk of systemic exposure to the vector. The safety of CTL102 has been demonstrated in single dose and in repeat dose studies in the mouse and in local tolerance studies in the rat. Administered intravenously in single doses up to  $8.5 \times 10^{10}$  particles/ml at a dose volume of 200  $\mu$ L per animal, CTL102 was well tolerated and at higher doses resulted in some liver damage, reflected by increased liver weight, enzymes and histological effects.

In monkeys CB1954 was injected intravenously. The elimination half-lives (1.5 h) indicate there is rapid clearance of the prodrug from the plasma. Clearance is probably both hepatic and renal. In general, doses given to mice intravenously represent a 1-2  $\times 10^3$  fold safety margin over the same dose given in humans.

To assess local tolerance CB1954 was injected subcutaneously in male CD-1 mice. High doses were injected (1.5, 6, and 24 mg/kg). As a controls group either the vehicle (5% N-methyl pyrrolidone, 17.5% PEG300 and 77.5% physiological saline) or physiological saline alone was injected. No local responses considered to be related to treatment with CB1954 were evident at macroscopic or microscopic examination of the

injection site or local lymph nodes. It was concluded from this study that a single subcutaneous administration of CB1954 to male CD-1 mice at dosages up to 24 mg/kg, was well tolerated, and was without local effect in the subcutis at the injection site or local lymph nodes.

#### *Pharmacokinetic characteristics*

Pharmacokinetic results indicate that CB1954 has a mean volume of distribution of 14.2 litres/m<sup>2</sup> (range 12.8-18.5 liters/m<sup>2</sup>), a half-life of about 18 minutes (range 4-35 minutes) and clearance values (range 0.7-1.5 liters/min), which approximate hepatic blood flow.

#### **Summary of findings from clinical studies with adenovirus gene transfer vectors and CB1954**

In 1999 18-year-old Jesse Gelsinger died after a direct infusion of an Ad-vector in the right hepatic artery. He received  $3.8 \times 10^{13}$  Ad-vector particles, the highest dose ever injected in humans. After reviewing clinical and post-mortem findings as well as other related studies, members of the Working Group concluded that the research participant's death most likely resulted from a systemic, Ad vector-induced shock syndrome. A cytokine cascade led to disseminated intravascular coagulation, acute respiratory distress, and multi-organ failure. Post-mortem bone marrow biopsy revealed red cell aplasia. The data suggested that the high dose of Ad-vector delivered by infusion directly to the liver, quickly saturated available receptors for the vector within that organ and then spilled into the circulatory and other organ systems, including the bone marrow, thus inducing a systemic response.<sup>8</sup>

After the tragical death of Jesse Gelsinger doses given to patients by intravenous route were limited to  $10^{11}$  Ad-vector particles. Besides, safety criteria for clinical grade adenovirus vector preparations were established, including the criteria of being free of endotoxin and infectious agents and containing  $\leq 1$  replication-competent adenovirus (RCA) for the total dose to be delivered.

In 2002 Harvey and Crystal brought out two lengthy reports concerning the safety and toxicity of local delivery of low ( $<10^9$  particles)- and intermediate ( $10^9$ - $10^{11}$  particles)-dose adenovirus gene transfer vectors in humans. The studies analyse the adverse events (AE), abnormal laboratory parameters, and deaths observed in 8 trials involving a total of 140 local administrations of low and intermediate doses of adenovirus gene transfer vectors to 6 sites in 90 individuals. The total experiences from the 8 trials were grouped to determine whether 10 putative risk factors could be predictive of the safety of trials. The risk factors were structured in 3 groups, associated

with the individual (age, sex, comorbid index<sup>21</sup>, and pretherapy anti-Ad antibody titer), adenovirus vector (dose, route of administration, transgene in the expression cassette, and number of vector administrations), and the gene transfer trial (trial design and involvement of major surgery in the trial). It was found that only the comorbid index was a predictor of death. For major adverse events other than death, age and whether surgery was part of the trial were determined to be predictors. As no significant association of vector-related factors with major adverse events is seen, it is suggested that local administration of these doses of HAdV-5 vectors appear to be well tolerated. For all studies combined, the most common abnormal laboratory parameters were a low haemoglobin (13.7%) and elevated WBC (12.8%), both occurring mostly in association with surgery and returning to normal values within 30 days. Abnormal laboratory values were mostly seen in participants over 50 years of age and the number of adverse events increased with age. Anti-HAdV-5 neutralising antibody did not appear to be associated with any aspect of AE or abnormal laboratory parameter. The frequency of AEs and abnormal laboratory results slightly increased with HAdV-5 vector dose.<sup>26,55</sup>

There are several differences from the experimental animal studies discussed earlier and the human Ad5 vector trials by Crystal *et al.*<sup>26</sup> in which no association could be found between vector dose and major adverse events. First, most studies demonstrating major 'toxicity' of HAdV-5 vectors in experimental animals use doses  $10^2$ - to  $10^3$ -fold greater per kilogram body weight than the doses used in the human studies. Second, all the routes used in the human study were local, whereas most experimental animal studies use systemic administration. Third, in all human studies HAdV-5 vector preparations were thoroughly controlled before injection. Finally, HAdV-5 vectors may interact differently with blood elements of humans from that of animals.

25 patients with operable liver, head/neck or prostate tumours have been injected intra-tumourally with CTL102 at doses ranging from  $10^8$  to  $5 \times 10^{11}$  particles. No treatment-related serious adverse events have been observed. ELISAs to detect viral proteins have been conducted on urine, stools and plasma samples 24 h after injection, and the results showed no detectable shed virus at any dose. Following surgical resection of tumours in these patients Ntr expression has been monitored by immunohistochemistry on tumour sections. Dose-dependent Ntr expression has been observed, and at the higher doses Ntr expression observed in >30% of all sections through the tumours from several patients.

Toxicity of CB1954 prodrug was tested<sup>23</sup> in humans receiving intraperitoneal doses of 3, 6, 12, 18, and 24 mg/m<sup>2</sup> and intravenous doses of 3, 6, 12, 18, 24, 30, and 37.5 mg/m<sup>2</sup>. There was mild transient treatment-related toxicity due to CB1954 observed in local (i.p.) and systemic (i.v.) administration of doses up to 24 mg/m<sup>2</sup>. In

intravenous administration dose limiting toxicity occurred at a dose of 37.5 mg/m<sup>2</sup>. 24 mg/m<sup>2</sup> is the CB1954 dose selected for the CTL102/CB1954 clinical studies as giving adequate plasma levels without toxicity.

In this clinical study CB1954 will be injected intra-articularly ensuring optimal exposure to the target tissue. Due to the small particle size of CB1954, the particles will probably leak out of the joint soon. However, when a dose of 24 mg/m<sup>2</sup> is injected in the relatively small joint the concentration will probably, for a short duration, be so high that it is toxic on its own. However, for efficient killing of the interface cells, a sufficiently high concentration is needed for a sufficiently long period. Therefore we take the advantage of good exposure to the interface cells over the possible toxicity. Patients will be given up to the maximum systemic dose, which is 24 mg/m<sup>2</sup>. The dose will be limited by the volume of the periprosthetic space and the solubility of the CB1954 (2 mg/ml).

After five patients the dose was lowered to 16 mg/m<sup>2</sup> in conformity with protocol amendment 2 (03 Feb 2005) due to gastro-intestinal side effects and rise in liver transaminases.

#### Summary of known and potential risks and benefits

Safety observations found in human studies with other HAdV-5 viral vectors are confirmed with animal studies on CTL102:

- HAdV-5 vector leakage into the systemic circulation from the site of intratumoural administration gives rise to transgene delivery to the liver (mainly), as well as the spleen, kidney and lung.
- Leakage from the administration site increases with the speed of injection, as well as with the dose of the vector.
- The presence of anti-HAdV-5 neutralising antibodies tends to be ubiquitous in human adults and can be induced in animal models by simple exposure to the wild-type virus (e.g. intranasally). Such neutralising antibodies severely reduce accidental/incidental liver transduction by up to 1000-fold while peak transgene-expression was only reduced by 2.4-fold in the tumours of immune animals in intratumoural viral vector injection.<sup>15</sup> Varnavski *et al.*<sup>123</sup> performed a study to assess the impact of pre-existing immunity to HAdV-5 on the activation of innate immune responses to systemically administered HAdV-5 vector. They found that levels of IL-6 in serum after vector administration were higher in pre-immunised rhesus monkeys, relative to those in naïve animals. They concluded that the pre-existing immunity increased the activation of innate immunity. However, the HAdV-5 dosage used in the study is a sub-lethal dose; it is not clear whether a lower dose would render the same

results. Furthermore, only two monkeys are used in both groups, and the question is whether the same results would be found in larger groups.

- Possible local toxicity of high concentration of CB1954. Possible local toxicity will not be monitored, because invasive interventions are needed to evaluate this. However, we don't expect local toxicity as subcutaneous injection of CB1954 into mice at a dose of up to 24 mg/kg did not result in toxic effects at the injection site judged macroscopically.

#### *Expected adverse events during the study*

Intra-articular injection in the hip may cause moderate pain in the joint.

#### *Rare events during the study*

As with any therapy, rare side effects cannot be excluded beforehand. Occasional reports of the following adverse events have been made:

- When using strict aseptic techniques there is a risk of approximately 0.01% that an infection will occur after intra-articular injection. If infection occurs, this complication will be treated with antibiotics and drainage.
- Allergic reactions to contrast medium can occur
- In the case of systemic exposure to significant amounts of CTL102 healthy tissues infected by the viral vector will also express Ntr and could sustain damage following CB1954 exposure. The liver is in principal at greatest risk of damage as the liver takes up the majority of blood borne virus.
- From studies it cannot be fully excluded that transgene products can be integrated in germ cells, although animal studies show no integration. Therefore, patients will be expected to practice contraception for 80 days. This is the period of time in which CTL102 can be detected in gonads after administration of the viral vector.

#### *Potential benefits*

If gene therapy is successful and interface tissue is destroyed, patients can experience benefits from participation in the study. Bone cement injected into the periprosthetic space can then probably stabilise the endoprosthesis, thereby improving ADL-function (ADL = activities in daily living) and reducing pain from the loosened prosthesis.

#### **Description and justification of route of administration and dosage**

To optimise local delivery of the vector and prodrug to the interface tissue, these products will be injected intra-articularly in the diseased hip. Because of the large differences in the size of virus and prodrug, these agents will act differently. The virus has a

large particle size and when the HAdV-5 vector is administered in the joint space, most of the viral vector will probably stay there. As the joint space is a more or less closed system, shedding of the virus to other body compartments will be minimised. Therefore, local administration will give less systemic adverse effects than systemic administration. Moreover, in local administration the same dosages (compared to systemic administration) will give better therapeutic effects. The periprosthetic space is accessible to joint fluid (especially in aseptic loosening) and cells injected intra-articularly can thus probably reach target cells (interface cells). During screening period, only patients are included with an arthrogram confirming that the contrast medium is easily distributed in the total periprosthetic space. As in these patients the contrast medium is distributed through the entire periprosthetic space we expect that the viral vector and prodrug will also be distributed throughout this area. To establish a sufficiently high concentration of CTL102 we will only include patients in the study in which a small to medium arthrography volume ( $\leq 30$  ml) will give sufficient exposure of the interface tissue to the vector. Although arthrography is a rather invasive procedure in the patient group to be included, we consider it the only possible way to prove accessibility of the entire periprosthetic space.

The distribution of CB1954 is a rather different story. CB1954 is a very small molecule and will thus easily diffuse from the injection site. To assure optimal exposure of the prodrug to the transduced interface cells the maximal systemic CB1954 dosage without treatment-related toxic side effects is used. This dose ( $24 \text{ mg/m}^2$ ) will be administered in one injection in the hip joint\*. During a short period a very high concentration of CB1954 will be present in the joint. This high dose is possibly toxic on its own (in non-infected cells) and may cause death of some non-infected cells. However the highest possible dose is needed to assure a sufficiently high concentration for a sufficiently long period.

As this is a phase I study treatment will start at a low dose of virus. Earlier studies showed no serious adverse events when using local administration of  $<10^{11}$  HAdV-5 vector particles in humans. In this study no dosages of  $>10^{11}$  particles will be administered. First three patients will be injected with  $3 \times 10^9$  particles. When no dose-limiting toxicity (DLT) occurs for at least 14 days, the next three patients will be injected with a dosage of  $1 \times 10^{10}$  particles. Dose limiting toxicity is defined as any grade 3 or 4 adverse event except for nausea and vomiting. In this way dosage increment will continue to a dose of  $3 \times 10^{10}$  particles and finally  $1 \times 10^{11}$  particles will be given to the last three patients. When DLT occurs in 1 patient of three, three more patients will be included in

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\* After five patients the dose was lowered to  $16 \text{ mg/m}^2$  in conformity with amendment 2 (03 Feb 2005).

the same dose. When no other DLT occurs in these patients, the dose will be increased. When DLT occurs in 2 or more of the six patients, the given dose will be the maximal administered dose and three more patients will be included in the previous dose group. When DLT occurs in 2 or more patients of three, no more patients will be included in this dose group.

CB1954 prodrug will be injected intra-articularly 48 h after administration of the viral vector. Previous studies have been done in ML Laboratories to observe optimal transduction duration of CTL102. It was shown in animal studies that peak expression level of nitroreductase (Ntr) was obtained 48 h after intravascular or intratumoural injection of CTL102.

In earlier studies optimal CB1954 dosage without treatment-related toxic side effects was found to be 24 mg/m<sup>2</sup>. In our *in vitro* studies we pointed out that a CB1954 concentration of 50 µM for 24 h gives cell viability of <20% in vector concentrations of 200 pfu/cell. Chung-Faye *et al.*<sup>23</sup> studied toxicity of CB1954 in humans using intravenous and intra-peritoneal injections. In intravenous injection, a dose of 24 mg/m<sup>2</sup> gave a peak serum concentration of 6.3 µM. After 2 h the concentration had decreased to 1 µM. In intra-peritoneal injection, the same dose resulted in a peak concentration of 70 µM. After 18 h the concentration had dropped to 1 µM. As intra-articular injection has a small distribution area, we expect that a dose of 24 mg/m<sup>2</sup> will give a sufficiently high concentration (50 µM) during a sufficiently long period (24 h) to destroy interface cells. In order to maximise the likelihood of achieving adequate exposure of CTL102-infected interface cells to CB1954 the prodrug will be injected intra-articularly at a maximum dose of 24 mg/m<sup>2</sup>. The dose will be limited by the joint capacity and the maximum solubility of the prodrug (2 mg/ml), and will have a maximum of 24 mg/m<sup>2</sup>\*. Local toxicity is not expected to occur as the prodrug will leak out of the joint space rapidly following injection. Indeed, because of this rapid efflux it will be essential to inject as much prodrug as possible. Consistent with this, subcutaneous injection of CB1954 into mice at a dose of up to 24 mg/kg did not result in toxic effects at the injection site judged macroscopically and microscopically. Systemic toxicity will not occur as this dose has been shown to be well tolerated when administered by intravenous and intraperitoneal routes.

### Preparation of treatments

Treatments will be prepared in a clean room within the section IGFL (Interdivisional GMP facility LUMC) (GMP (=good manufacturing practice) facility), being part of the department of Clinical Pharmacy and Toxicology, by a specially trained and authorised

\* After five patients the dose was lowered to 16 mg/m<sup>2</sup> in conformity with amendment 2 (03 feb 2005).



person. Preparation, transport and other actions done with the vector will be performed according to the safety regulation appended.

It is not possible to blind the results. Patients have to be injected in increasing dosages to assess treatment-related toxicity. It is therefore not necessary to label the treatments in a manner in which dosage is blinded from investigators.

#### **Procedures for monitoring subject compliance**

Study medication (HAdV-5 vector and CB1954) will be administered under direct supervision. Two investigators will check the medication label for agreement of the contents with the study number and the subject's identity. After intra-articular injection, both investigators will sign the drug deposition form.

## **Methods**

#### **Trial design and sample size**

The study will be a Phase I, open-labeled, non-randomised trial. Patients who meet the inclusion- and exclusion-criteria will be asked to participate in the study. Informed consent will then be obtained from the study participants. Power estimations are not possible because there are no results from relevant earlier studies. The study scheme is outlined in table 1.

A total of 12 patients will be enrolled in the study. The first three patients will receive  $3 \times 10^9$  HAdV-5 vector particles, the second three will receive  $1 \times 10^{10}$  particles, the next three  $3 \times 10^{10}$  particles and the last three  $1 \times 10^{11}$  particles. The particles will be added to saline in a volume 10% less than the volume used at the inclusion arthrogram. This to prevent lymphatic drainage of the vector due to a high pressure, while creating a pressure high enough to allow the fluid to reach the periprosthetic space. Two days after injection of the viral vector (day 2) patients will receive CB1954 by intra-articular injection at a concentration of 2mg/ml. The total dose will depend on the arthrogram volume of the treated patient and will thus vary from patient to patient. The dose will, however, not exceed  $24 \text{ mg/m}^2$ \*. To minimise influence of synovial fluid on the vector and prodrug the joint will be extensively rinsed with 2 mM EDTA solution before administration of vector and prodrug. The EDTA will improve efficiency of gene transfer, whereas viability of the cells is not influenced. In a study by de Roos *et al.*<sup>31</sup> infection of liver cells increased from 21% to 54% after administration of EDTA. The

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\* After four patients the dose was lowered to  $16 \text{ mg/m}^2$  in conformity with amendment 2 (03 Feb 2005)

exact mechanism of the EDTA on the improvement of gene transfer is unknown, but it is assumed that the EDTA causes dissociation of the cells or widening of the fenestrae in the cell by binding of  $\text{Ca}^{2+}$ . After saturation of the EDTA by  $\text{Ca}^{2+}$  (from the interface cells and from the bone) and other metal ions, the effect on the cells is extinguished and EDTA is excreted by the kidneys. On day 9 interface biopsies will be taken to investigate efficacy of the interface destruction. The patient will undergo spinal anaesthesia and a thick needle is introduced in the bone through which the biopsy is taken (at three sites around the femoral stem and at one site in the acetabulum). The needle will then be used as an introduction site for the injection of bone cement (figure 1). Bone cement is injected in the periprosthetic space under fluoroscopic guidance to prevent leakage of the cement into the joint space.

Figure 1. Schematic outline of study

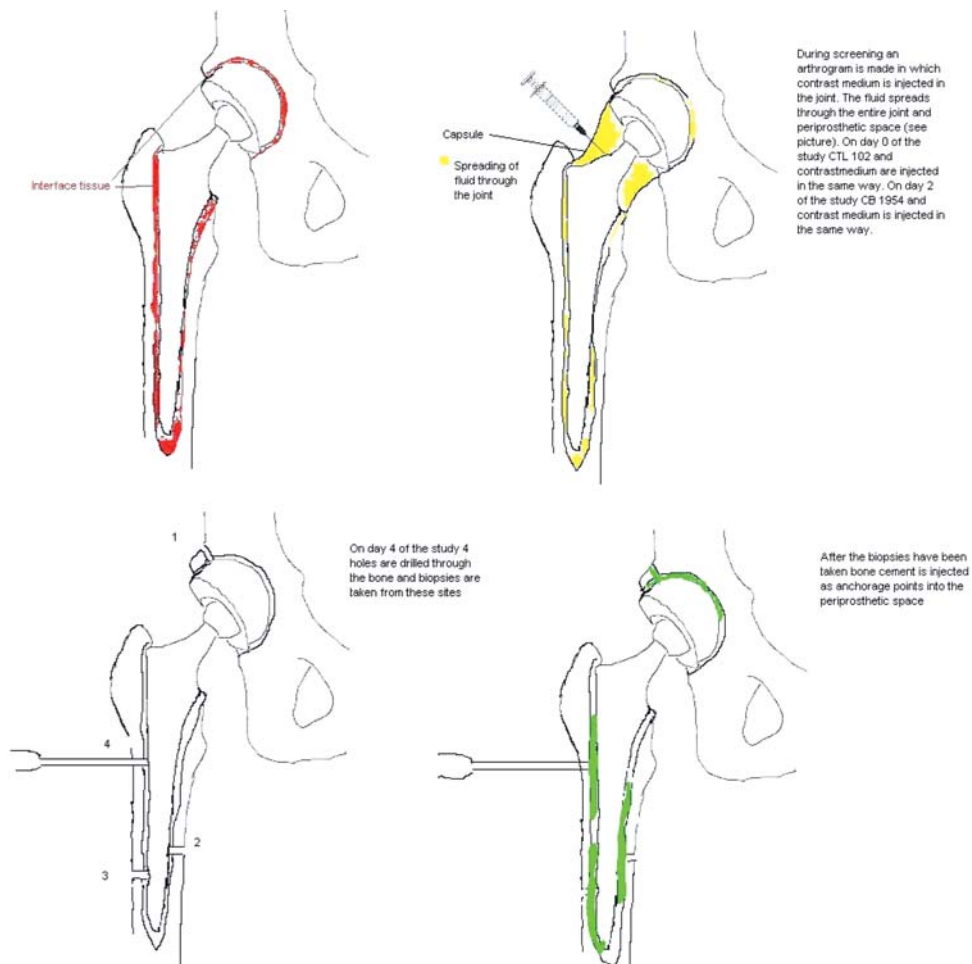


Table 1. Schematic presentation of frequency investigations

	Inclusion	0	1	2	3	4	5	6	7	8	9	10	4	6	3	6	1	1	every
		d	d	d	d	d	d	d	d	d	d	d	w	w	m	m	y	y	year
History, physical examination, AEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RR and Temp	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ad5.Ntr injection	x																		
Arthrography	x	x																	
Xrays	x											x				x	x	x	x
CB-1954 injection																			
Blood sampling	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biopsies, cement stabilisation																			
Collection excreta																			
VAS for pain	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
VAS walking distance + independency, HHS	x																		

Abbreviations: d: day; w: week; m: month; y: year; HHS: Harris Hip Score; RR: blood pressure  
 Blood test: HB, HT, WBC and differentiation, platelets, ESR, CRP, creatinin, Na, K, Ca, Mg, albumin,  
 amylase, glucose, AST, ALT, LDH, Alk Phos, bilirubin and PT, PTT; CB1954 concentration (on day 2 (2x))  
 a: whenever earlier samples were positive

## Primary study endpoints

### *Adverse events*

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the intervention. Adverse events reported by the patient or observed by the researcher or other investigators will be subscribed and classified according to intensity, duration and time of occurrence. All adverse events will be recorded on the adverse event data collection form.

For each event the relationship to drug (definite, probable, possible, unknown, definitely not) as judged by the investigator, as well as eventual actions taken, will be recorded. The occurrence of an adverse event that is fatal, life-threatening, disabling or requires or prolongs in-patient hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly of birth defect will be described according to Clinical Trials Directive 2001/20/EC as 'serious adverse event (SAE)'. The responsible investigator will report SAEs as follows:

- All SAEs will be reported to ML Labs. plc. by telephone and in writing as soon as practical, but at least within 24 h of recognition;
- All SAEs will be reported by the investigator to the Medical Ethics Review Board and the CCMO that approved the study, by telephone and in writing as soon as practical, but at least within 15 days;
- SAEs with a suspected (probable or definite) relationship to trial medication (as indicated by the responsible investigator) will be reported to the Drug Safety Unit of the Healthcare Inspectorate ('Hoofdinspectie voor de Farmacie en de Medische technologie, Inspectie voor de Gezondheidszorg').

Reports to the Health Authorities are submitted in conjunction with ML Labs. plc. ML Labs can prepare additional reports for other authorities.

### *Safety parameters*

Blood pressure, temperature and 22 laboratory parameters (see below) are measured. We specifically chose these parameters because they are relevant to laboratory abnormalities observed in experimental animals receiving high doses of HAdV-5 vectors. Abnormality of laboratory parameters will be classified according to WHO recommendations for grading of acute and sub-acute toxic effects.

- *General safety measurements*

After HAdV-5 vector administration the researcher will visit the patient at least according to the following scheme and whenever it is clinically indicated. In each visit medical history and physical examination (inspection of injection-area and auscultation of heart and lungs) will be done. Furthermore, vital signs will be recorded.

Visits to the patient will be made directly before and after viral vector injection, ½ hourly to 4 h, hourly to 8 h and 4-hourly to 24 h. After 24 h, visits will be made at 6 hourly intervals until CB1954 administration. Vital signs will then be recorded daily until discharge from the hospital, and at each assessment point throughout the study.

- *Safety laboratory measurements*

Hematology: The following assessments will be performed: Haemoglobin, hematocrit, ESR, white cell count (WBC), leukocyte differential count and platelet count.

Blood biochemistry: The following assessments will be performed: lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, glucose, amylase, bilirubin, creatinin, Na, K, Ca, Mg, albumin, CRP, partial thromboplastin time (PTT) and prothrombin time (PT). CB1954 concentration in the blood will be measured 5 minutes and 1 and 2 hours after administration.

Urine: In the patient's room a urinestick will be dipped in the urine to assess proteinuria and haematuria.

### Secondary study endpoints

- *Investigation of a biopsy of interface tissue after the procedure*

On day 9 of the study patients will undergo an interface tissue biopsy under spinal anaesthesia. Interface tissue biopsies will be done using Jamshidi needles. From biopsy holes interface tissue will be taken. The Pathology laboratory will describe the histological appearance of the interface tissue and compare it to interface tissue derived during revision surgery.

- *Endpoints to exclude shedding of the virus and prodrug*

To assess whether any of the vector was shed from the target organ systemically or in the environment patients will be monitored on blood, urine, pharyngeal, nasal, and rectal samples. Samples will be collected for PCR analysis 24 h after CTL102 injection, and daily until negative results are obtained. CB1954 concentration is measured in the blood 5 minutes and 1 and 2 h after administration.

- *Endpoints to investigate stabilisation of the prosthesis in the femur*

X-rays will be made to estimate periprosthetic space before and after the procedure. X-rays will be made at screening and one day after cement injection, after 6 months and then every year.

- *Endpoints to investigate clinical results of the study*

Pain, independency and walking distance

Pain experienced by the patient will be measured by using a Visual Analogue Scale (VAS). In this, patients are asked to score the pain they experience on a gliding

scale. The scale is a 10 cm long line, at the left beginning with 'no pain at all' and at the right ending with 'unbearable pain'. Patients can score their pain by placing a mark on the gliding scale. In the same manner a visual analogue scale will also be used to quantify independency and walking distance.

Ability to walk/ improvements in ADL

Improvements of ADL-function will be measured using the Harris Hip Score. In this score performance is measured on the following items: pain, limp, support, walking distance, stair climbing, putting on socks and shoes, sitting, and ability to use public transport.

#### **Withdrawal of individual subjects**

Subjects can leave the study at any time and for any reason if they wish to do so without consequences. The responsible investigator can also withdraw a subject if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the patient or the investigator
- Refusal of the patient to continue treatment and/or observations
- Any infection after vector administration, not intended in the study
- Unacceptable or dose limiting toxicity
- Decision by the investigator that termination is in the patient's best medical interest
- Unrelated medical illness or complication
- Loss to follow-up
- Death of patient (will be reported to the researcher by the general practitioner)

#### **Replacement of individual subjects after withdrawal**

Patients who withdraw from the study will not be replaced by other patients.

#### **Follow up of subjects withdrawn from treatment**

Patients withdrawn from treatment will preferably be followed up in the same manner as other patients in the study. When patients withdrawn from the study don't consent to further follow up a last analysis is done to investigate whether there are any toxic effects at that moment (laboratory parameters and adverse events) and whether there is any viral shedding to the environment (urine, faeces, blood, and nose and throat swabs). In abnormality of parameters necessary actions will be taken to secure safety for the patient and the environment.

### Discontinuation criteria for the study

The study will be discontinued when an unacceptable adverse event occurs, that is definitely or probably related to the procedures in the study.

## Data analysis

### Data handling and record keeping

Data will be recorded first on a paper Case Record Form (CRF) and then on a spreadsheet in which all patient's data are listed. After validation data will be entered in a computer system for subsequent tabulation and statistical analysis. The data will be handled confidentially and anonymously. All patients who enter the trial will be analysed, the patients who complete the trial as well as patients who withdraw from the study after injection of the virus and prodrug.

### Statistical analysis

Statistical analysis will be performed at the Department of Orthopaedic Surgery in the LUMC.

Means and standard deviations will be used to describe outcome parameters, supplemented by calculation of confidence intervals wherever this aids interpretation. A  $p$  - value of  $<0.05$  will be considered significant. Graphical presentations will be made in which patterns of adverse events are displayed.

Laboratory parameters will be subjected to linear regression in which 1.25 x upper normal value is taken as upper limit of normal values. Also a linear regression is done in which a 25% difference between baseline and follow-up values is taken as upper limit for normal variation.

## Appendix 1. WHO-recommendations for grading of toxic side effects

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<b>Hematological</b>					
Leukocytes (x10 <sup>9</sup> /L)	4.0 – 20.0	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	< 1.0
Thrombocytes (x10 <sup>9</sup> /L)	≥ 100	75 – 99	50 – 74	25 – 49	< 25
Hemoglobin (mmol/L)	≥ 7.5	6.2 – 7.4	5.0 – 6.1	4.0 – 4.9	< 4.0
Granulocytes (x10 <sup>9</sup> /L)	≥ 2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
Lymphocytes (x10 <sup>9</sup> /L)	≥ 2.0	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
Hemorrhage	None	Mild, no transfusion needed	Gross, 1–2 units transfusion needed	Gross, 3–4 units transfusion needed	Massive, > 4 units transfusion needed
<b>Coagulation</b>					
Prothrombin time (sec)	≤ 14	14.1 – 17.5	17.6 – 21	21.1 – 28	> 28
APTT (sec)	≤ 33	33.1 – 54.8	54.9 – 76.9	77 – 99	> 99
<b>Metabolic</b>					
Hyperglycemia (mmol/L)	< 6.4	6.4 – 8.9	9.0 – 13.9	14.0 – 27.8	> 27.8
Hypoglycemia (mmol/L)	> 3.6	3.1 – 3.6	2.2 – 3.0	1.7 – 2.1	< 1.7
Amylase (U/L)	50 – 220	221 – 330	331 – 440	441 – 1100	> 1100
Hypocalcaemia (mmol/L)	< 2.72	2.72 – 2.95	2.96 – 3.21	3.22 – 3.44	> 3.44
Hypocalcaemia (mmol/L)	> 2.15	2.00 – 2.15	1.79 – 1.99	1.56 – 1.78	< 1.56
Hypomagnesaemia (mmol/L)	> 0.57	0.49 – 0.57	0.37 – 0.48	0.25 – 0.36	< 0.25
<b>Gastrointestinal</b>					
Nausea	None	Reasonable intake	Decreased intake, but able to eat	No significant intake	-----
Vomiting	None	1 episode in 24 h	2 - 5 episodes in 24 h	6 - 10 episodes in 24 h	> 10 episodes in 24 h or parenteral support required
Diarrhea	None	Increase 2 - 3x/ day	Increase 4 – 6x/ day or nocturnal stools or moderate cramping	Increase 7 – 9x/ day or incontinence or severe cramping	Increase > 10x/ day or bloody diarrhea or parenteral support required
Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers, able to eat solids	Painful erythema, edema, or ulcers, and cannot eat solids	Needs parenteral support for alimentation



	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<b>Liver</b>					
Bilirubin ( $\mu\text{mol/L}$ )	$\leq 17$	-----	17 – 25	26 – 51	$> 51$
AST (U/L)	5 – 40	41 – 100	101 – 200	201 – 800	$> 800$
ALT (U/L)	5 – 45	46 – 112	113 – 224	225 – 896	$> 896$
Alkaline phosphatase (U/L)	40 – 120	121 – 300	301 – 600	601 – 2400	$> 2400$
Liver clinical	No change	-----	-----	Pre-coma	Hepatic coma
<b>Renal</b>					
Creatinine ( $\mu\text{mol/L}$ )	70 – 133	134 – 200	201 – 400	401 – 800	$> 800$
Proteinuria	No change	1+ or 3g/L	2+/3+ or 3 - 10g/L	4+ or $> 10\text{g/L}$	Nephritic syndrome
Hematuria	Negative	Microscopic	Macroscopic, no clots	Macroscopic + clots	Transfusion or cystectomy required
Weight loss	$< 5\%$	5.0 – 9.9%	10.0 – 20.0%	$> 20.0\%$	-----
<b>Pulmonary</b>					
	No change	Asymptomatic, with abnormality in PFTs	Dyspnea when exercising	Dyspnea at normal level of activities	Dyspnea at rest
<b>Cardiac</b>					
Cardiac arrhythmias	none	Asymptomatic, transient, no treatment needed	Recurrent or persistent, no treatment needed	Treatment required	Monitoring required, or hypotension or VT or VF
Cardiac function	No change	Asymptomatic, decline in resting EF $< 20\%$ of baseline value	Asymptomatic, decline in resting EF $> 20\%$ of baseline value	Mild CHF, responsive to treatment	Severe or refractory CHF

## Appendix 2. Harris Hip Score

### HARRIS HIP SCORE

#### I PAIN (MAX 44 POINTS)

None or ignores it	44 pt
Slight, occasional, no compromise in activities	40 pt
Mild pain, no effect on average activities, rarely moderate pain with unusual activity, may take aspirin	30 pt
Moderate pain, tolerable but makes concessions to pain. Some limitations of ordinary activity or work. May require occasional pain medication stronger than aspirin	20 pt
Marked pain, serious limitation of activities	10 pt
Totally disabled, crippled, pain in bed, bedridden	0 pt

#### II FUNCTION (MAX 47 POINTS)

##### Walking (max 33 points)

##### *Limp*

None	11 pt
Slight	8 pt
Moderate	5 pt
Severe	0 pt

**Support**

None	11 pt
Cane for long walks	7 pt
Cane most of the time	5 pt
One crutch	3 pt
Two canes	2 pt
Two crutches	0 pt
Not able to walk (specify reason)	0 pt

**Distance walked**

Unlimited	11 pt
500 – 1000 m	8 pt
100 – 500 m	5 pt
Indoors only	2 pt
Not able to walk	0 pt

**Activities (max 14 points)**

**Stairs**

Normally without using a rail	4 pt
Normally using a rail	2 pt
In any matter	1 pt

Unable to do stairs 0 pt

***Shoes and socks***

With ease 4 pt

With difficulty 2 pt

Unable 0 pt

***Sitting***

Comfortably in ordinary chair one hour 5 pt

On a high chair for one-half hour 3 pt

Unable to sit comfortably in any chair 0 pt

***Enter public transportation*** (if yes) 1 pt

**III ABSENCE OF DEFORMITIES (MAX 4 POINTS)**  
(If all are applicable 4 points, otherwise 0 points)

Less than 30° fixed flexion contracture

Less than 10° fixed adduction

Less than 10° fixed internal rotation in extension

Limb-length discrepancy less than 3.2 cm

**IV RANGE OF MOTION (MAX 5 POINTS)**

## Appendix 3. Patient information

### Patient information for a scientific study of gene therapy as an experimental treatment in a loosened hip prosthesis.

Responsible investigator: Prof. Dr. R.G.H.H. Nelissen  
Department: Orthopaedic surgery  
Telephone: 071-5263606

Dear Sir, Madam,

In continuation of the consult with your own orthopaedic surgeon you hereby receive information in writing about a scientific study in which we ask your cooperation.

We do not ask you to make a decision immediately. Do take some time for reflection before you decide to contribute to the study. We advise you to discuss your co-operation with your family, general practitioner or others.

Would you feel any need to put your questions to a doctor that is not directly involved in the study, you can find the name and telephone number of this independent doctor in these information pages.

#### Introduction

As was discussed with you, the prosthesis in your hip has loosened. Therefore, you have complaints of pain in the hip and walking difficulty. Usually the treatment for this loosening is an operation. In this operation the old prosthesis is taken out and a new one is put in. In some patients (including you) the risk for adverse events during such an operation is high. That is why we are searching for alternative treatments to refix a loosened prosthesis.

We asked your contribution in a study with a new, not yet registered, gene therapy. To gain more information about safety, tolerability and optimal dosing of this experimental treatment, studies in patients are necessary.

In animal studies with this form of gene therapy the adverse events were limited up till now. There have been limited studies in humans. About the safety and tolerability of the treatment, the following can be stated: The doses of the treatments used in patients in this study have not caused serious adverse events in other studies.

#### Study objectives

From previous studies we know that certain inflammatory cells, which break down the bone around the prosthesis, cause prosthesis loosening. Up till now there are no

medications that can stop these inflammatory cells. By means of gene therapy we are aiming to remove these inflammatory cells. The effect is as follows:

Gene therapy is a new experimental treatment, which is thoroughly investigated at the moment. With gene therapy you can give certain cells specific instructions. An adenovirus (which normally causes a cold) is used to deliver this instruction into the cell (like a letter). We need the virus, because the letter is not able to go to the cell on its own. As a virus normally enters the cells, it can well be used to deliver the message. Before, the virus was modified so that it is not able to multiply. All information that the virus uses to make people ill, is removed. The virus only knows how to penetrate the cell, and that it has to deliver a message.

In this study a virus is used that penetrates the inflammatory cells (which cause the loosening) efficiently. These cells get the instruction to make a certain protein in an amount as high as possible. After 2 days a drug is administered to the joint that specifically destroys the cells that have produced a high quantity of the protein. The body then automatically clears these cells away. We investigated in our laboratory that we can kill the inflammatory cells in this way. But we don't know yet whether it also works in humans. We will now investigate what happens when the modified virus and the drug are injected in a patient with a loosened hip prosthesis. We will study whether there are adverse events and whether the virus can leak to the environment. And of course we want to know whether the inflammatory cells can be destroyed by the gene therapy. We also want to know if we can put bone cement in the space where the inflammatory cells were, to refix the prosthesis.

The study will take place in the Leiden University Medical Center (LUMC) and a total of 12 patients will participate in the study.

### **Design of the study**

The participating patients will be divided in 4 groups. Each group will receive a different amount of virus to see which dose is the best. First three patients receive the lowest dose. Then these patients are followed during 2 weeks to see whether they have adverse events. Only after this period the second group receives a higher dose, etc.

When you want to participate in the study history is taken and physical examination will be done. Also blood will be drawn and X-rays of your hip are made. These investigations have to be done to see whether you are a good candidate for the study. If you appear to be an appropriate candidate and you still want to participate, an examination will be done in which contrast fluid is injected in the hip joint and X-rays (arthrography) will be made to see how loose the prosthesis is. If you are going to participate in the study appointments will be made for the days when you are expected in the hospital for examinations.

During the study you will be admitted to the hospital for 11 days, of which the first few days in an isolated room. The first day of your admission the virus will be injected in your hip joint. On the third day the drug, that will destroy the inflammatory cells, will be injected in the same way. To see whether the therapy was successful four holes will be drilled through the bone around the prosthesis. Because the bone cannot be anaesthetised you will have spinal anaesthesia. Through the drilled holes some of the inflammatory tissue will be removed to examine whether the cells were destroyed. Furthermore, we will inject bone cement through these holes to refix the prosthesis. During the 11 days of your admittance to the hospital several examinations will be done to investigate whether there are adverse events from the treatment. Just like in other medications the body can react to the therapy and you can have adverse effects. From the moment that the virus is administered, someone will check on you every 30 minutes, and measure blood pressure and temperature. When you are doing fine, controls will be phased out. To trace down potential adverse effects as soon as possible blood will be drawn on day 2 and 5 for laboratory analysis. To check that the virus will stay in the hip joint and does not migrate through the body and the environment extra examinations will be done. Therefore, you will be asked to cooperate to examination of urine, faeces, nose and throat swabs and blood. During the year after your admission to the hospital you will visit the out-patient clinic 7 times to check on clinical effects of the treatment.

### **Potential risk of the study**

As this form of treatment with gene therapy is new, the experience is still limited. This study will be done to track down potential adverse effects. Up till now there are no indications that the virus will shed outside the injected joint. Still, to prevent every potential shedding of the virus, the virus will be injected in an isolated room. A sample of your blood, faeces, urine and sputum will be collected after one day and analysed for presence of virus, and every day until negative results. You are asked to stay in your room until we know for sure that there is no virus in your urine, faeces, sputum or blood.

During the study you will have two injections in your hip joint, once to administer the virus, and once to administer the prodrug. Injections in the joint can be painful. After injection there is a minimal risk to infection.

On the fifth day of the admission, 4 small holes will be drilled in the bone (under spinal anaesthesia). Through these holes through a thick needle, a piece of bone and inflammatory tissue will be removed for analysis (biopsy). Through the same needle bone

cement will be injected in the open space between prosthesis and bone. The injection from the spinal anaesthesia can be painful. There is a small chance that you experience a headache after the spinal anaesthesia. The cuts in your skin are so small that you don't need any stitches.

#### **Potential benefits from the study**

If the inflammatory cells, which are responsible for the loosening of the prosthesis, turn out to be destroyed by the gene therapy, and if the space between bone and prosthesis can be filled with bone cement, you could possibly experience a benefit from participation in the study. As this study is the first one in which gene therapy is used to treat loosening of prostheses, there are no results from previous studies available. The results, which will proceed from this study are difficult to predict. That is why you'd better anticipate that you won't experience any benefits from participation in the study.

#### **Blood transfusion and organ donation**

The Minister of VROM (environment) has stated that patients who participate in a gene therapy study are not allowed to donate blood for blood transfusion. In case of organ donation the physicians need to be informed about the gene therapy study you participated in. Although it is unlikely that the virus will still be present in an organ, they want to rule out the possibility that the virus will be transferred by blood transfusion or organ donation. You therefore have to sign a written declaration.

#### **Voluntary participation**

Your participation to the study is voluntarily. If you decide to cooperate in this study, you have the opportunity to come back at your decision at any moment. You don't have to give any argumentations, but you are asked to report your decision to your physician as soon as possible. He will discuss with you whether discontinuation has any consequences for you that make it necessary to start another treatment. Your physician can also decide to discontinue your participation to the study, when he thinks this is better for your well-being. When this is the case your physician will discuss this with you. When, during the study, new information becomes available, your physician will discuss this with you. The decision to participate or not to participate in the study won't have any influence on the understanding you have with your physician.

#### **Financial compensation**

When you make extra travelling expenses because of participation of the study, these will be compensated.



### Confidentiality of data

You can be assured that all data that are accumulated under code (i.e. without report of your name and address) about you, will be handled confidentially according to the medical treatment agree (WGBO (*this is a Dutch law in which patient-physician relation is made clear*)) and that non-competent outsiders don't have access to your data. The results of this study will be used in a scientific publication, but also then the data will not be reducible to you as a person. We will inform your general practitioner about your participation in the study.

### Insurance

The LUMC has effected an insurance to cover potential damage inflicted by the study. When you think you have experienced damage from participation in the study you can contact the researcher.

### In conclusion

Would you have any questions regarding the information of this study you can ask your physician, the researcher and the independent physician.

For general information on participation in scientific studies we refer to the brochure "Asked for medical scientific research" (*this is a brochure which patients can ask at the information desk*), which is available at the patients-service-bureau on the second floor of the LUMC.

When you decide to participate in this study we ask you, at the next visit with reference to the study, to sign the informed consent form. By signing this form you are not committed to anything (your signature is not binding), but you give to understand that you have received and understood the information and that you know what is expected from you with regard to the study.

Researcher	JJ de Poorter	Indep. physician	Dr. CF Allaart
Department	Orthop. Surgery	Department	Rheumatology
Telephone	071-5263606	Telephone	071-5263598

## **Outline of all burdening of the study**

During hospital admittance:

**Injections in the joint:** To administer the virus and the drug as close as possible to the inflammatory cells (which cause the loosening) they are injected into the joint. This will take place in the radiology department. First, the skin will be anaesthetised and then the fluid will be injected using a thin needle. The injection can be painful. Injections will take place on the first and third day of the hospital admittance.

**Bone biopsies and injection of cement:** On the seventh day of the admittance four small holes are drilled through the bone to collect a little inflammatory tissue and cement is injected to refix the prosthesis. Because the bone cannot be anaesthetised locally you will have spinal anaesthesia. In total this will take about one hour. After the procedure you will be taken back to your room.

**Collection of urine, faeces, nose and throat swabs and blood** (These are called excreta). These investigations will be done to find out where the virus sheds after we have injected it. A sample of the urine and faeces you produce will be collected after 24 h after the injection of the virus and will be analysed for presence of virus. Also, with a piece of cotton-wool, a culture will be taken from your nose and throat and a blood sample will be taken. All samples will be evaluated as soon as possible. The next day samples will be taken again if virus was present the previous day. When all samples are free of virus, you are allowed to leave the room whenever you want.

**Adverse effects:** To track down potential adverse effects of the gene therapy you will be observed carefully. We do this by asking you questions about how you are feeling and by physical examinations (listening to heart, lungs and abdomen and palpation of the abdomen). Also, blood samples will be taken to investigate whether you have adverse effects you haven't mentioned. The physical examinations will take place every day, the blood samples will be taken on the second day and the fifth day.

**Hospital visits:** In the first part of the study you will be admitted to the hospital during 11 days. You will have a separate room. During the first days you are not allowed to come out of the room. Nevertheless you are allowed to receive visitors.

Until 1 year after the injections you will visit the researcher in the hospital a total of 7 times for this study. During the visits she will ask you whether there are any problems or complaints and she will do physical examinations. The traveling-expenses you make for visiting the hospital will be compensated. The researcher can arrange that a taxi will collect you at home and bring you back after the visit, if you like that.

**Blood samples:** The first three times that you visit the hospital for the study you will be asked to have 2 tubes of blood drawn. This will be done to investigate whether there are adverse effects that you haven't mentioned. Whenever possible, potential adverse effects will be treated. Three months and 1 year after the injections in the hip joint another tube of blood is taken to investigate how the immune system has responded to the gene therapy.

**X-rays:** To investigate whether the treatment was successful some X-rays will be made. At the last day of your admittance an X-ray will be taken from your hip and pelvic region (these pictures are the standard pictures you have had before). In the control visits after 2 weeks, after 6 months and after 1 year similar pictures are taken.

The burdening you may experience from the study is outlined in the scheme on the next page.



## Appendix 4. Patiënten-informatie

**Patiënteninformatie ten behoeve van een wetenschappelijk onderzoek naar genterapie als experimentele behandeling bij een losgelaten heupprothese.**

Versie 5, 29 september 2003

Verantwoordelijk onderzoeker: Dr R.G.H.H. Nelissen  
Afdeling: Orthopaedie  
Tel.: 071-5263606

Geachte mevrouw, mijnheer,

In aansluiting op het gesprek met Uw behandelend arts ontvangt U hierbij de schriftelijke informatie met betrekking tot een wetenschappelijk onderzoek waarvoor Uw medewerking is gevraagd.

Wij vragen U niet om onmiddellijk een beslissing te nemen. Neemt U rustig enige bedenktijd voordat U beslist of U meedoet of niet. Wij raden U aan om Uw deelname te bespreken met Uw partner, familie, huisarts of anderen.

Mocht U behoefte hebben Uw vragen voor te leggen aan een arts die niet direct bij dit onderzoek betrokken is, dan kunt U de naam en het telefoonnummer van deze onafhankelijk arts vinden op de vijfde pagina van deze informatie.

### Inleiding

Zoals met U besproken is, is de prothese in Uw heup los gaan zitten. Daardoor heeft U klachten als pijn in de heup en moeite met lopen. Meestal wordt als behandeling bij zo'n losse prothese een operatie gedaan. Bij deze operatie wordt de oude prothese eruit gehaald en wordt er een nieuwe ingezet. Bij sommige mensen (en ook bij u) is de kans op nadelige gevolgen van zo'n operatie echter te groot. Daarom zijn we op zoek naar andere methoden om een losse prothese vast te zetten.

Wij hebben U gevraagd medewerking te verlenen aan een onderzoek met een nieuwe, nog niet geregistreerde genterapie. Voor het verkrijgen van meer informatie over de veiligheid, verdraagbaarheid en juiste dosering van deze experimentele behandeling zijn onderzoeken bij patiënten noodzakelijk.

Bij dierexperimenteel onderzoek met genterapie met dit soort virus zijn de bijwerkingen tot op heden beperkt gebleken. Er is in beperkte mate onderzoek bij mensen gedaan. Wat betreft de veiligheid en verdraagbaarheid van de therapie uit dit onderzoek kan het volgende worden gezegd: De hoeveelheden van het middel dat in dit onder-

zoek bij patiënten wordt ingespoten hebben bij andere onderzoeken niet gezorgd voor ernstige bijwerkingen.

### **Doel van het onderzoek**

Uit eerdere onderzoeken die gedaan zijn weten we dat een prothese loslaat doordat bepaalde ontstekingscellen het bot afbreken dat rond de prothese zit. Tot nu toe zijn er geen medicijnen die deze ontstekingscellen kunnen tegenhouden. Door middel van gentherapie willen we deze ontstekingscellen verwijderen. Dit werkt als volgt:

Gentherapie is een nieuwe experimentele behandeling waar momenteel veel onderzoek naar wordt gedaan. Met gentherapie kun je specifieke cellen een opdracht uit laten voeren. Er wordt een verkoudheidsvirus gebruikt om deze opdracht (als een soort brief) af te leveren in de cel. Het virus is nodig, omdat de boodschap niet vanzelf de cel in kan. Aangezien een virus normaal ook cellen binnendringt, kan hij goed gebruikt worden om de boodschap in de cel te bezorgen. Het virus is van tevoren wel zo aangepast dat het zich niet meer kan vermenigvuldigen. Daardoor is de kans dat mensen ziek worden van het virus veel kleiner. Het virus weet alleen nog hoe het in de cel moet komen en dat hij de opdracht moet afgeven.

In dit onderzoek wordt een virus gebruikt dat onder andere naar de ontstekingscellen gaat die de loslating van de prothese veroorzaken. Deze cellen krijgen dan als opdracht om zoveel mogelijk van een bepaald eiwit te maken. Na 2 dagen wordt er een medicijn ingespoten dat specifiek de cellen kapot maakt die heel veel van het eiwit hebben gemaakt. We verwachten dat we deze cellen daarna uit de ruimte kunnen wegspoelen en dat een gedeelte van de cellen vanzelf door het lichaam wordt opgeruimd. We hebben in het laboratorium onderzocht dat we op deze manier de ontstekingscellen onschadelijk kunnen maken. Maar we weten nog niet of het ook bij mensen werkt. Nu zal onderzocht worden wat er gebeurt als we het aangepaste virus en het medicijn bij patiënten met een loszittende prothese inspuiten.

We gaan onderzoeken of mensen er geen bijwerkingen van krijgen en of het virus niet in de omgeving terecht komt. En natuurlijk willen we ook weten of de ontstekingscellen kapot gemaakt kunnen worden met de gentherapie. Tevens willen we onderzoeken of we in de ruimte waar eerst de ontstekingscellen zaten, botcement kunnen spuiten om de prothese weer vast te zetten.

Het onderzoek vindt plaats in het LUMC te Leiden en in totaal zullen 12 patiënten deelnemen.

### **De opzet van het onderzoek**

De deelnemende patiënten zullen in 4 groepen worden verdeeld. Iedere groep krijgt een andere hoeveelheid virus ingespoten om te kijken welke hoeveelheid het beste

is. De eerste drie patiënten krijgen de laagste dosis. Dan wordt gedurende minimaal 2 weken gekeken of zij geen bijwerkingen krijgen. Pas daarna krijgt de tweede groep een hogere dosis ingespoten, enz.

Voordat het onderzoek begint worden, als U mee wilt werken aan het onderzoek, een aantal gegevens van U genoteerd, U wordt lichamelijk onderzocht, er worden 2 buisjes bloed afgenomen en er worden röntgenfoto's van Uw heup gemaakt. Als blijkt dat U een geschikte kandidaat bent voor de studie en U wilt nog steeds meedoen, wordt een onderzoek gedaan waarbij een contrastvloeistof in het heupgewricht gespoten wordt en er röntgenfoto's worden gemaakt om te kijken hoe los de prothese zit (arthrografie). Als U mee gaat doen in het onderzoek worden er afspraken met U gemaakt over dagen dat U in het ziekenhuis verwacht wordt voor het onderzoek.

Tijdens het onderzoek wordt U 11 dagen opgenomen in het ziekenhuis, waarvan ongeveer de eerste vier dagen op een eenpersoonskamer. De eerste dag krijgt U het virus in het heupgewricht gespoten. Op de derde dag krijgt U het medicijn ingespoten dat de cellen kapot moet maken. Om te kijken of de therapie succes heeft gehad worden er op de negende dag vier gaatjes geboord door het bot rond de prothese (3 in het bovenbeen en 1 in het bekken). Als verdoving krijgt U hierbij een ruggeprik. Via de geboorde gaatjes wordt wat van het ontstekingsweefsel weggehaald om te onderzoeken of de cellen kapot zijn gegaan. Bovendien gaan we via deze gaatjes nieuw botcement inspuiten om de prothese weer vast te zetten.

Tijdens de 11 dagen dat U opgenomen bent worden er verschillende onderzoeken gedaan om te kijken of er bijwerkingen zijn van de behandeling. Net zoals bij medicijnen kan het lichaam reageren op de therapie en kunt U bijwerkingen krijgen. Vanaf het moment dat het virus ingespoten is komt er ieder half uur iemand bij U langs om te informeren hoe het met U gaat en om bloeddruk en temperatuur te meten. Als het goed met U gaat zullen de controles wat minder vaak gedaan worden. Om eventuele bijwerkingen zo snel mogelijk op te sporen wordt ook een aantal keer bloed afgenomen voor laboratoriumonderzoek. Dit gebeurt op dag 2 en 5. Om te controleren dat het virus alleen in de heup blijft en dat er niets 'lekt' naar de rest van het lichaam en de omgeving worden extra onderzoeken gedaan. Daarom wordt U gedurende de studie regelmatig gevraagd mee te werken aan lichamelijk onderzoek en aan de controle van bloed, urine, ontlasting en een keel- en neusuitstrijk. U zult in het jaar na de opname nog zeven keer gecontroleerd worden op eventuele bijwerkingen van de behandeling.

#### **De eventuele risico's van het onderzoek**

Omdat deze vorm van behandeling met gentherapie nieuw is, is de ervaring nog beperkt. Deze studie is bedoeld om eventuele bijwerkingen op te sporen.

Tot nu toe zijn er geen aanwijzingen dat het virus zich buiten het ingespoten gewricht

zal verspreiden. Toch zal, om elke mogelijke verspreiding van het virus te voorkomen, het virus ingespoten worden op een eenpersoonskamer op de afdeling reumatologie. Uw ontlasting, urine en speeksel zullen opgevangen worden en onderzocht worden op aanwezigheid van het ingespoten virus. Het is de bedoeling dat U Uw kamer niet verlaat totdat wij zeker weten dat er geen virus in Uw urine, ontlasting of speeksel zit.

Tijdens deze studie zult U 2 maal in Uw heupgewricht geprikt worden, eenmaal om het virus in te spuiten en eenmaal om het medicijn in te spuiten. Injecties in het gewricht kunnen pijnlijk zijn. Na injectie in een gewricht bestaat een minimaal risico op een infectie.

Op de tiende dag van de opname worden 4 gaatjes in de huid gemaakt (verdoofd met een ruggeprik). Via deze gaatjes wordt via een dikke naald een stukje bot en ontstekingsweefsel weggehaald (biopsie). Via dezelfde naald wordt daarna botcement in de open ruimte tussen prothese en bot gespoten. De ruggeprik kan pijnlijk zijn. Er is een kleine kans dat U hoofdpijn krijgt na de ruggeprik. De gaatjes in de huid zijn zo klein dat ze niet gehecht hoeven te worden.

#### **Mogelijke voordelen van het onderzoek**

Als zou blijken dat de ontstekingscellen die verantwoordelijk zijn voor het loslaten van de prothese kapot gemaakt kunnen worden door de genterapie en als de ruimte tussen de prothese en het bot opgevuld kan worden met botcement, zou U mogelijk een gunstig effect kunnen ondervinden van deelname aan het onderzoek. Omdat dit onderzoek het eerste is waarbij genterapie gebruikt wordt om loslating van prothesen te behandelen zijn er nog geen resultaten uit andere onderzoeken beschikbaar. De resultaten die uit deze studie zullen voortkomen zijn moeilijk te voorspellen. Daarom kunt U er beter vanuit gaan dat U geen voordelen zult ondervinden van deelname aan de studie.

#### **Bloedtransfusie en orgaandonatie**

De minister van VROM heeft bepaald dat patiënten die aan een genterapie studie deelnemen geen bloed voor bloedtransfusie mogen afstaan. In geval van orgaandonatie voor transplantatiedoeleinden dienen de artsen geïnformeerd te worden over de genterapie. Alhoewel het onwaarschijnlijk is dat het virus nog in een orgaan aanwezig is, wil men uitsluiten dat het virus door bloedtransfusie of orgaantransplantatie wordt overgedragen. U dient hiervoor een schriftelijke verklaring te ondertekenen.

#### **Vrijwilligheid van deelname**

Uw medewerking aan dit onderzoek is vrijwillig. Als U toestemming geeft om aan dit



onderzoek mee te doen, heeft U te allen tijde de vrijheid om op die beslissing terug te komen. U hoeft hiervoor geen reden op te geven, wel wordt U gevraagd dit direct aan Uw behandelend arts te melden. Hij zal dan met U bespreken of het stoppen van het onderzoek consequenties voor U heeft die het eventueel nodig maken een andere behandeling te starten.

De eerste dagen na injectie in het gewricht zult U verzocht worden op Uw kamer te blijven. Uw ontlasting, urine en speeksel worden in deze dagen onderzocht op uitscheiding van het virus om te onderzoeken of U mogelijk mensen in Uw omgeving zou kunnen besmetten met het virus. Het is belangrijk voor de mensen in Uw omgeving dat U zich niet uit de studie terugtrekt gedurende deze periode. Na deze periode staat het U vrij op elk moment te stoppen met deelname aan het onderzoek.

Ook Uw behandelend arts kan Uw deelname aan het onderzoek stopzetten als deze vindt dat dit ten aanzien van Uw gezondheid beter is. Uw arts bespreekt dit dan met u. Wanneer tijdens het onderzoek nieuwe informatie bekend wordt, zal Uw behandelend arts dit eveneens met U bespreken.

Het wel of niet meedoen heeft op geen enkele wijze gevolgen voor de verstandhouding met Uw arts.

### **Vergoeding**

Wanneer U in het kader van deelname aan het onderzoek extra reiskosten maakt, worden deze vergoed.

### **Vertrouwelijkheid van de gegevens**

U kunt ervan verzekerd zijn dat alle gegevens die tijdens dit onderzoek onder code (d.w.z. zonder vermelding van Uw naam en adres) over U verzameld worden, vertrouwelijk behandeld worden volgens de wet geneeskundige behandelingsovereenkomst (WGBO) en dat niet-bevoegde buitenstaanders geen inzage hebben in Uw gegevens. De resultaten van dit onderzoek worden gebruikt in een wetenschappelijke publicatie, maar ook dan zijn de gegevens niet tot U als persoon herleidbaar.

De stukjes ontstekingsweefsel die via de boorgaten worden verwijderd zullen bewaard worden. Met dit weefsel kan later eventueel nog onderzoek gedaan worden. De arts-onderzoeker zal aan U toestemming vragen om de stukjes ontstekingsweefsel te bewaren. Ook vragen wij U toestemming om Uw huisarts op de hoogte te stellen van Uw deelname aan het onderzoek en andere informatie die wij van belang vinden. Ook vragen wij U of wij Uw huisarts informatie mogen vragen over Uw vroegere en huidige ziekten.

### **Verzekering**

Er is door het LUMC een verzekering afgesloten waaruit eventuele schade als gevolg

van het onderzoek betaald kan worden. Wanneer U vindt dat U schade heeft ondervonden als gevolg van deelname aan het onderzoek kunt U contact opnemen met de arts-onderzoeker. Informatie over de afgesloten verzekering treft U aan in de bijlage.

**Tot slot**

Mocht U naar aanleiding van deze informatie nog vragen hebben met betrekking tot dit onderzoek dan kunt U daarmee terecht bij Uw behandelend arts, de arts-onderzoeker of de onafhankelijk arts.

Voor algemene informatie over deelname aan wetenschappelijk onderzoek verwijzen wij U naar de brochure "Gevraagd voor medisch-wetenschappelijk onderzoek", die verkrijgbaar is bij het patiëntenservicebureau op de tweede etage van het LUMC.

Wanneer U besluit aan dit onderzoek deel te nemen vragen we U bij het eerstvolgende bezoek aan het ziekenhuis in het kader van dit onderzoek een handtekening te zetten (het informed consent). Met de ondertekening verplicht U zich nergens toe (Uw handtekening is niet 'bindend'), maar geeft U te kennen dat U deze informatie ontvangen en begrepen heeft en weet wat er van U verwacht wordt met betrekking tot het onderzoek.

Artsonderzoeker: JJ de Poorter  
Afdeling: Orthopedie  
Telefoonnummer: 071-5263606

Onafhankelijk arts: Dr CF Allaart  
Afdeling: Reumatologie  
Telefoonnummer: 071-5263598

Verantwoordelijk onderzoeker:  
Afdeling:  
Tel.:

Dr R.G.H.H. Nelissen  
Orthopaedie  
071-5263606

## De belasting van het onderzoek op een rijtje

Tijdens de ziekenhuisopname:

**Injecties in het gewricht:** Om het virus en het medicijn zo dicht mogelijk bij de ontstekingscellen (die zorgen voor de loslating van de prothese) te brengen worden ze in het gewricht ingespoten. Dit gebeurt op de röntgenafdeling. Eerst wordt de huid verdoofd en daarna wordt met een dun naaldje de vloeistof ingespoten. De injectie kan pijnlijk zijn. De injecties vinden plaats op de eerste en derde dag van de ziekenhuisopname.

**Botbioptieën en inspuiten van cement:** Op de negende dag van de ziekenhuisopname worden vier gaatjes door het bot geboord om een beetje ontstekingsweefsel weg te halen en wordt cement ingespoten om de prothese vast te zetten. Omdat het bot niet verdoofd kan worden met een lokale verdoving krijgt U een ruggeprik. Om zo hygiënisch mogelijk te werken zal dit alles op de operatiekamer gebeuren. In totaal zal dit ongeveer een uur duren. Daarna wordt U terug naar Uw kamer gebracht.

**Verzamelen van urine, ontlasting, keel- en neuskweken en bloedonderzoek** (Dit worden excreta genoemd). Deze onderzoeken worden gedaan om te onderzoeken waar het virus blijft nadat we het hebben ingespoten. De urine en ontlasting die U produceert worden gedurende de eerste 24 uur verzameld en er wordt onderzocht of er virus in zit. Verder wordt met een wattenstokje een kweek genomen uit de keel en uit de neus en wordt een keer bloed afgenomen. Al deze onderzoeken worden zo snel mogelijk beoordeeld. De volgende dag worden alleen de excreta verzameld waar de vorige dag nog virus zat. (Bij voorbeeld als in Uw bloed en ontlasting geen virus was aangetoond hoeft U dit niet meer in te leveren). Als nergens meer virus in zit mag U de kamer weer verlaten wanneer U dat wilt.

**Bijwerkingen:** Om eventuele bijwerkingen van de gentherapie op te sporen wordt U zorgvuldig geobserveerd. Dit gebeurt door aan U te vragen of U klachten heeft en door lichamelijk onderzoek (luisteren naar het hart, de longen en de buik en voelen aan de buik). Daarnaast wordt ook bloed geprikt om te onderzoeken of er bijwerkingen zijn waar U zelf nog niets van merkt. Het lichamelijk onderzoek gebeurt iedere dag, de bloedafnames gebeuren op de tweede dag (2 keer ) en op de vijfde dag (1 keer).

**Bezoeken aan het ziekenhuis:** In het begin van het onderzoek wordt U gedurende 11 dagen opgenomen in het ziekenhuis. U ligt dan op een eenpersoonskamer. Gedurende de eerste dagen mag U Uw kamer niet verlaten. U mag natuurlijk wel bezoek ontvangen. Tot 1 jaar na het onderzoek wordt U in totaal 7 keer op de polikliniek orthopedie verwacht bij de arts-onderzoeker. Hierna komt U een

keer per jaar op controle bij Uw behandelend orthopaed. Tijdens de poliklinische bezoeken informeert de arts-onderzoeker hoe het met U gaat en of er problemen zijn. Ook wordt gevraagd of U mee wilt werken aan een kort lichamelijk onderzoek. De reiskosten die U maakt om naar het ziekenhuis te komen worden vergoed. Als U dat wilt kan de arts-onderzoeker een taxi voor U regelen die U thuis ophaalt en na het polibezoek weer naar huis brengt.

**Bloedafnames:** De eerste 3 keer dat U op de polikliniek komt wordt U gevraagd om na het polibezoek bloed te prikken (2 buisjes). Dit wordt gedaan om te kijken of er bijwerkingen zijn van de behandeling waar U zelf niets van merkt. De arts-onderzoeker belt U een paar dagen later thuis op om de uitslag van het bloedonderzoek te bespreken. Als het mogelijk is worden eventuele bijwerkingen behandeld. 3 Maanden en 1 jaar na de ziekenhuisopname wordt nog 1 buisje bloed afgenomen om te onderzoeken hoe het immuunsysteem heeft gereageerd op de gentherapie.

**Röntgenfoto's:** Om te onderzoeken of de behandeling succes heeft gehad worden een aantal röntgenfoto's gemaakt. Op de laatste dag van de ziekenhuisopname worden een foto van het bekken en van de heup gemaakt (zoals U die wel eerder hebt laten maken bij polikliniekbezoeken). Bij de nacontroles na 2 weken, na 6 maanden en na 1 jaar worden nogmaals dezelfde foto's gemaakt.

**De belasting die U zult ondervinden van het onderzoek is samengevat in het schema op de volgende pagina.**

**Schema voor het onderzoek**

Eerste onderzoek	Ziektehuisopname										Poli-bezoeken						
	Dag 1	Dag 2	Dag 3	Dag 4	Dag 5	Dag 6	Dag 7	Dag 8	Dag 9	Dag 10	Na 2 weken	Na 4 weken	Na 6 weken	Na 3 mnd	Na 6 mnd	Na 1 jaar	ledr jaar
Lichamelijk onderzoek, vragenlijst	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Injectie in gewricht	x		x														
Bloedafnames	x	x	x	x													
Verzamelen urine, ontlasting, keel- en neuskweken	x	x	x	x													
Röntgenfoto's	x																