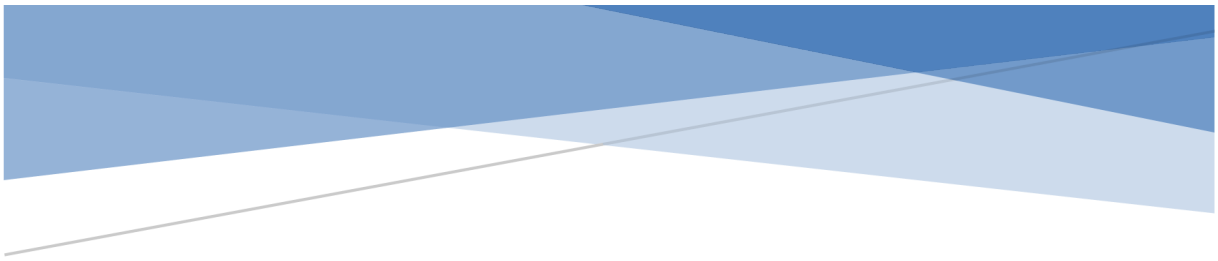

Grip on knee **O**A: **DI**straction **V**ersus **A**rthroplasty **(GODIVA)** for young knee-osteoarthritis patients in routine care.

Research protocol v2.0, including add-on study on bone

d.d. 17-08-2023

PROTOCOL TITLE 'Grip on knee OA: DIstraction Versus Arthroplasty (GODIVA) for young knee-osteoarthritis patients in routine care.

Protocol ID	**NL78932.041.21**
Short title	**GODIVA**
EudraCT number	Not applicable
Version	**V2.0**
Date	**17-08-2023**
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Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
EULAR	**European League Against Rheumatism**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
KJD	**Knee Joint Distraction**
KP	**Knee Prosthesis**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
StWP	**State of knowledge and clinical practice**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**

TKP	**Total Knee Prosthesis**
UKP	**Unicompartmental Knee Prosthesis**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
VAS	**Visual Analogue Scale**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: For relatively young (≤ 65 year) patients with severe knee osteoarthritis (OA) with persistent pain, insufficiently responding to conservative therapy and joint preserving surgery ('end-stage knee OA') a knee prosthesis (KP) is currently the most commonly used treatment. When a first prosthesis is placed at a young age, patients often need revision surgery later in life. Revision surgery is complex, costly, and accompanied by multiple complications. The increasing life expectancy, focus on patient empowerment, and the wish to stay active and independent up to high age, is anticipated to further increase the number of revision surgeries. As such, preventing revisions surgery is key. When a first prosthesis is placed after the age of 65, data show that the need for revision surgery becomes significantly lower.

Knee joint distraction (KJD) is a joint preserving treatment that significantly postpones the need for a primary knee prosthesis (up to ~ 10 years in 50% of cases). KJD is proven to be effective in reducing pain and stiffness and improving function, although effects seem slightly less compared to a knee prosthesis. As assessed by 'Zorg Instituut Nederland', KJD is promising but the current evidence still too limited and thus not yet suitable for reimbursement. Even in case KJD is less effective, if this is clinically acceptable (non-inferior), the reduced chance for burdensome revision surgery might still make it a treatment of choice.

With respect to the GODIVA-bone add-on study: i) Reaching a well-balanced decision made by patient and surgeon together (shared decision-making) on whether to be treated with knee distraction or not, based on a scientifically justified chance for success of knee distraction treatment, is key for future implementation of knee distraction. ii) A more in-depth insight in the relationship between peri-articular bone changes and improvement in pain perception and cartilage repair may add to development and/or improvement of new and existing treatment strategies for knee osteoarthritis directed towards bone.

Objective: To determine whether KJD is non-inferior on patient reported effectiveness as compared to a KP (i.e. usual care) for relatively young patients with end-stage knee OA. In the GODIVA bone substudy, the primary objective is to predict the benefit from knee distraction treatment by peri-articular bone characteristics. The secondary objective of the substudy is understanding the change in peri-articular bone in relation to the benefit from knee distraction treatment (pain relief and cartilage repair) by expanding the pre-treatment data with follow-up data.

Study design: Pragmatic, open, randomized, multi-centre, non-inferiority trial with 24 months follow-up.

Study population: 1,200 knee OA patients ≤ 65 year of age, indicated for a KP will be randomized (1:1) to KJD or KP. For the GODIVA-bone substudy: 200 patients from the 600 patients randomised to treatment with knee distraction in the GODIVA trial will be included.

Intervention (if applicable): KP is indicated and surgically implanted according to regular clinical practice (can be a total- or unicompartmental KP, in line with local practice in consultation with the patient and conform the national guideline by Dutch orthopaedic society (NOV)). KJD treatment is performed according to the current approved concept NOV recommendations for clinical practice.

Main study parameters/endpoints: Primary endpoint: Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score. Main secondary outcomes: WOMAC/KOOS Pain, stiffness, and physical function sub-scores, quality of life (EQ-5D, SF-36), radiographic joint space width (KJD only) as a surrogate for cartilage tissue repair; adverse events, and productivity and healthcare cost. All assessed over 24 months.

For the GODIVA-bone sub-study the main paramters are MRI, CT, and DEXA image markers and blood and urine biochemical markers at baseline and 24 months.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The benefit of a KP over KJD might be the swifter and slightly better clinical effect of treatment although at the expense of the original joint and with the higher risk of revision surgery later in life. The benefit of the KJD over a KP is that the original joint is preserved with the chance of postponing placement of a KP and decreasing the chance of revision surgery later in life, although with the burden of a 6-week distraction period with the chance of skin pin-tract infections, and possibly a slightly (non-clinically relevant) lesser clinical benefit.

In both arms, at 7 moments questionnaires must be filled out without the need of a clinic visit. At baseline for both treatments, and in case of KJD treatment additionally at 24 months a clinic visit takes place (the latter for a study specific x-ray) in addition to the typically 4 clinic visits performed in regular practice. In both arms a comparable number of knee radiographs is made in regular care and for KJD the 24 months study specific x-ray will be made.

In both arms the chance of failure is <5% in the first year after treatment. Failure can be due to multiple reasons, mostly persisting pain, leading to either revision surgery in case of a KP or placement of a first KP in case of KJD. Additionally, there is a chance of infection in both arms. In case of KJD these are primarily superficial skin pin tract infections, in generally successfully treatable with oral antibiotics. In both arms a small chance for deeper infections up to osteomyelitis are seen, needing i.v. antibiotics and/or nettoyage or even removal of the frame in case of KJD or early revision surgery in case of KP. Rehabilitation after the intervention(period) is similar for both treatment arms.

Patients randomised to knee distraction in the GODIVA trial are asked to participate in this GODIVA-bone add-on study. In case of consent, the burden will be a knee-MRI, knee-CT, and DEXA scan at pre-treatment and 2 years post-treatment, which will take two times an 60-120 min extra out-patient visit time. These image techniques are considered minimally

invasive with CT and DEXA with radiation exposure. Additionally, a vena puncture for 2 times 7 cc blood samples (serum and plasma) at both timepoints provides a minimal risk. The urine samples are considered riskless. There is no direct benefit for the patient.

1. INTRODUCTION AND RATIONALE

Knee osteoarthritis (OA) is a degenerative joint disease characterized by articular cartilage degeneration, periarticular bone changes, and soft tissue impairment causing pain, stiffness, and functional limitations, and considerable loss of quality of life (1,2). In the Netherlands, yearly almost 30,000 (total and unicompartmental) knee prostheses (KP) are placed for patients not sufficiently responding to conservative therapy or joint preserving surgery ('end-stage knee OA') (3).

About 30% of KP's are implanted under the age of 65. These patients have a significantly higher risk of revision surgery later in life, i.e., up to 35% and 20% in men and women, respectively in the age category 50-55 (4). When a first prosthesis is implanted after the age of 65, the need for revision surgery significantly decreases (see figure 1).

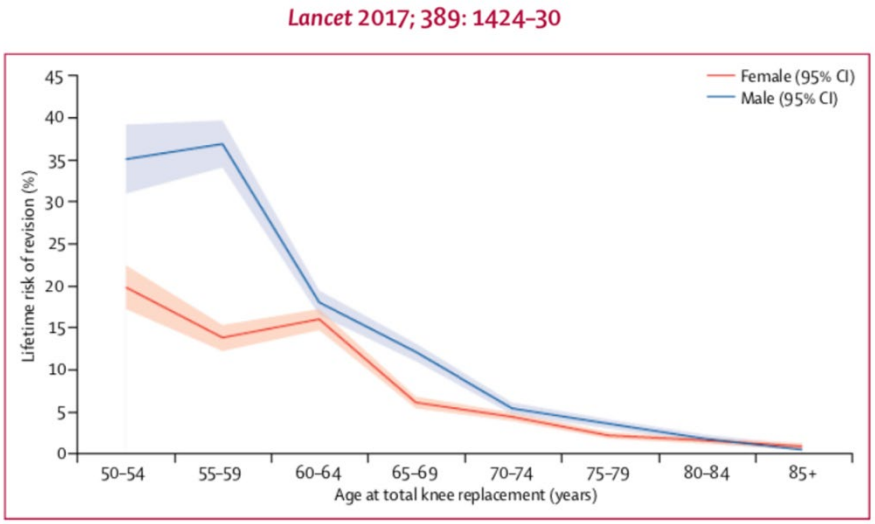
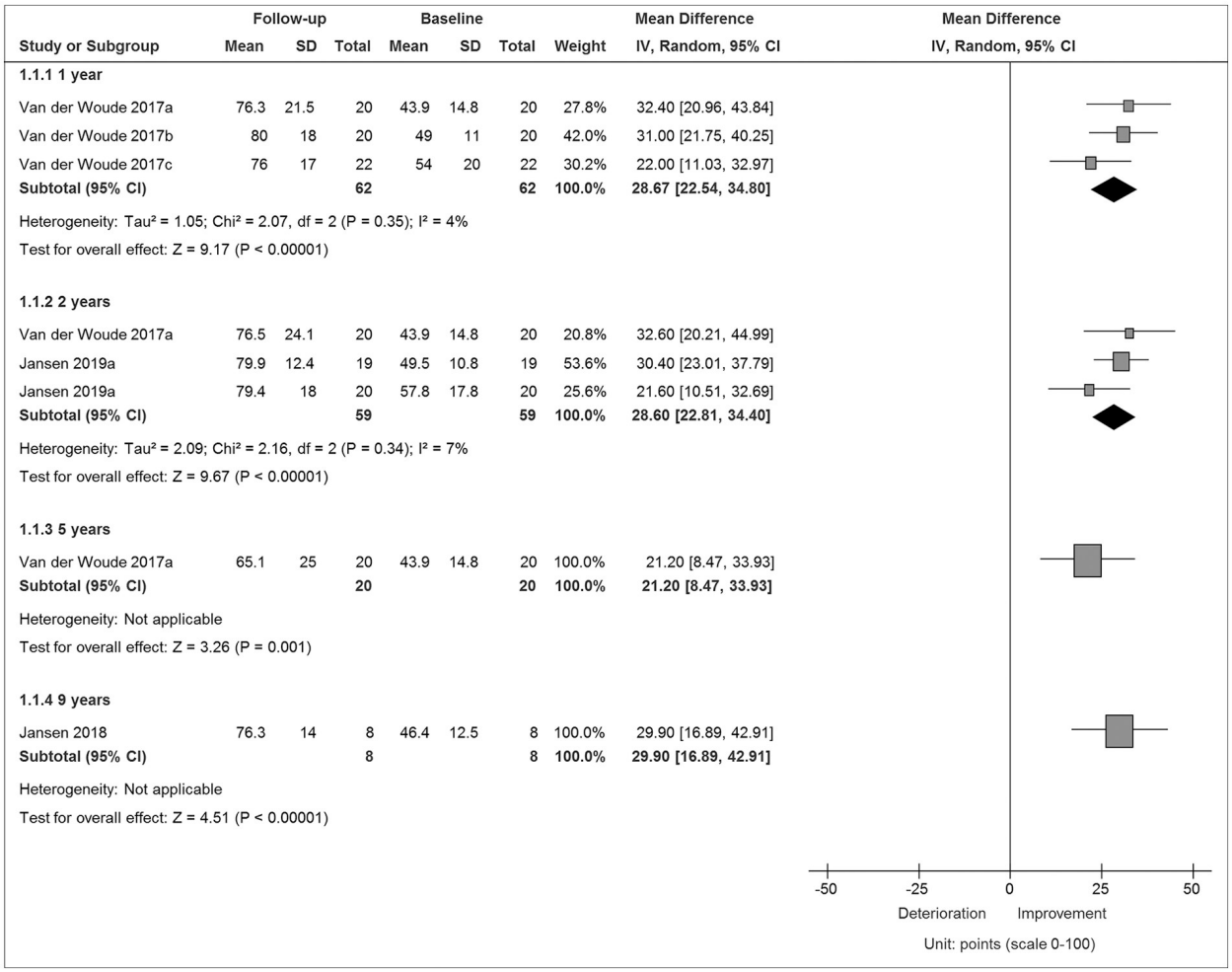


Figure 1 Lifetime revision rate of knee replacement

Revision surgery is complex, costly, and accompanied by multiple complications (5-7). With the increasing life expectancy, focus on patient empowerment, and the wish to stay active and independent up to high age, this problem is anticipated to further increase. Treatments that can postpone a KP are therefore desired.

Knee-Joint-Distraction (KJD) is such a treatment and uniquely demonstrates cartilage tissue repair (8,9) as well as amelioration of complaints. KJD places the two bony ends of the knee joint at a distance of about 5 mm for a period of about 6 weeks according to prescribed procedures as described and advised by the NOV (the Dutch orthopaedic society), see appendix S.



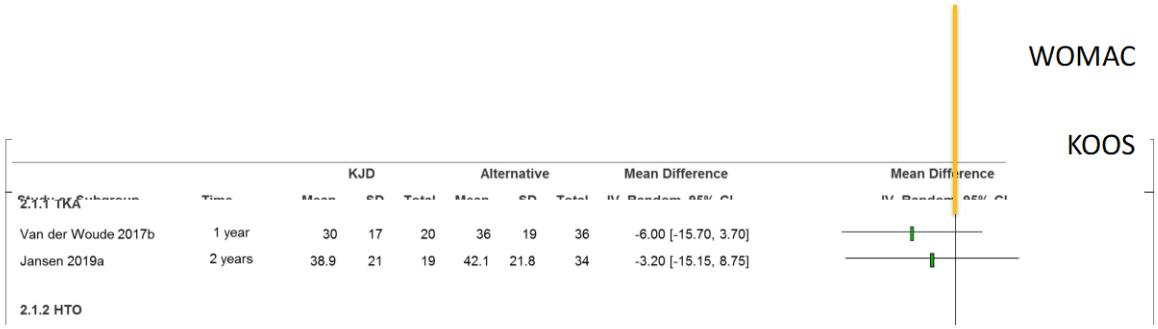
Several prospective studies and two RCTs have been performed. All KJD treated patients reached a ‘patient acceptable symptom state’ based on KOOS/WOMAC questionnaire domains and > 85% reached response according to modified OMERACT-OARSI criteria (own analysis) (8) see also table/figure above.

The mechanism behind its effect is still largely unknown but thought to be related to the absence of mechanical stress on the joint combined with intra-articular biochemical changes which allow damaged cartilage to repair itself (10).

Based on the data from previous research and preliminary combined analyses, bone parameters are considered key in response to knee distraction treatment. (Spil W et al,. Ann Rheum Dis 2013;72,) (Black A, J Orthop 2022;32,) (Curry Z et al. Menopause 2022;29,).;

Recently Zorg instituut Nederland (ZiN) performed an evaluation of the ‘state of knowledge and clinical practice (StWP)’ for KJD for the treatment of knee-OA indicated for a KP at a younger age (65 years). It was concluded that KJD is a promising treatment, but that the current evidence regarding this treatment is still insufficient for KJD to be eligible for reimbursement. Their judgement was mainly based on a small (n=20:40 patients) RCT comparing KJD to a total KP performed by our group (8). Patients showed no statistically

significant difference in patient reported efficacy outcomes between KJD and TKP, but the results seem to indicate that compared to KP, KJD is slightly less effective. See also table/figure below



This RCT was a comparison between KJD and a total KP. Roughly, there are two types of a knee prosthesis, a unicompartmental or total knee prosthesis. A total knee-prosthesis (TKP) has shown to be effective in reducing pain and regaining function. The average quality of life (utility) increases from 0.6 (preoperatively) to 0.85, indicating a substantial overall effectiveness (3). However, 20% of people are not satisfied and difficulties with kneeling and persisting pain commonly occur (4,6,7). Moreover, specifically when placed at a young age (<65 years), a significant number of patients will need revision surgery. Unicompartmental knee prostheses (UKP) are presently used in ~13% of all patients receiving a KP and specifically (in ~25%) in younger patients. Although, overall long-term results regarding revision rates are still less satisfactory, this may be due to the originally limited experience with the procedure. In centers implanting UKPs in higher numbers, UKP provides better long-term results that are comparable to TKP (11,12). Therefore, this type of KP is also suitable for younger patients.

2. OBJECTIVES

Primary Objective:

- To determine whether KJD is non-inferior to usual care (KP) regarding patient reported effectiveness as measured using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score (0-100; higher is better), over 2 years.

Secondary Objective(s):

- To determine whether KJD is non-inferior to usual care (KP) on patient reported effectiveness regarding secondary patient reported outcomes (e.g. WOMAC subscores for pain, disabilities and stiffness, quality of life) over 2 years.
- For KJD only: To determine the change in radiographic joint space width over 2 years compared to baseline (i.e. before KJD treatment) as a surrogate marker for cartilage tissue repair.
- To describe and compare adverse events between KJD and KP (including reoperations) over 2 years.
- In the **GODIVA-bone substudy**: to predict the beneficial effects of knee distraction treatment for patients with knee osteoarthritis, based on peri-articular bone characteristics.
- In the **GODIVA-bone substudy**: to elucidate the relationship between periarticular bone changes (pre- and 2 years post-treatment) and improvement in pain perception and cartilage repair.

Tertiary Objective:

- To describe and compare productivity and healthcare costs between KJD and KP over 2 years.
- To compare knee flexion over time

3. STUDY DESIGN

Pragmatic, open, randomized, multi-centre, non-inferiority trial. 1,200 patients who satisfy the eligibility criteria will be randomized 1:1 to receive KJD or KP as initial treatment. These patients will be followed for 24 months. Both strategies will be implemented in regular care in participating centers taking current NOV practice recommendations for both treatments into account. In general study visits coincide with regular care although some visits are specific for the study and most outcome information is collected digitally via e-mail. Patients will be included over a period of 2 years.

GODIVA-bone substudy: The GODIVA trial provides an ideal platform to add specific measurements for bone (imaging and biochemical) before and two years after treatment to a subset of patients who will be treated with knee distraction (n=200).
At least 7-10 participating centers (together scheduled for over 200 knee distractions in the GODIVA trial) have been identified based on the availability of (access to) the right imaging equipment enabling the proper image acquisition and infrastructure for blood sampling and processing.

4. STUDY POPULATION

4.1 Population (base)

Patients with knee OA considered for a KP according to regular clinical practice in line with NOV guidelines / recommendations without restrictions to undergo KJD.
Patients are treated in 14 orthopaedic centres according to local practice and expertise in line with NOV recommendations. All consecutive patients visiting the centres' outpatient clinics considered for KP and eligible for KJD are asked to participate.

GODIVA-bone substudy: In a selection of the participating centers all consecutive patients randomized to the knee distraction arm are asked to participate (up to 200 inclusions in total) in the GODIVA-bone substudy.

Below in-/exclusion for the study are in line with NOV guidelines for KP as well as the NOV (concept) recommendations for KJD in clinical practice (see appendix S).

4.2 Inclusion criteria

To be eligible to participate in this study, a subject must meet all the following criteria:
- Clinical diagnosis of knee OA
- Age ≤ 65 years and ≥ 18 years
- Persistent, refractory pain, insufficiently responding to conservative or previous surgical therapy
- Structural OA joint damage, indicated by a K&L grade of at least 2 as determined by the orthopedic surgeon in line with NOV recommendations.
- Able to wear an external fixator and care for it for 6 weeks
- Accepting that the maximal effect of KJD is not present directly after removal of the frame but may take months after frame removal
- Sufficient joint stability (according to the orthopedic surgeon's judgement)
- Flexion (>100 degrees) and extension range (<10 degrees)
- Weight and BMI <120 kg and <35 kg/m^2, respectively
- Sufficient understanding of the Dutch language
- Signed informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Primary patella-femoral knee osteoarthritis
- Surgical intervention in last 6 months
- Leg-axis deviation > 10 degrees (as determined by the orthopedic surgeon)
- Serious osteopenia making placing bone-pins and wearing a frame into a risk (according to the orthopedic surgeon's judgement)
- Coagulation problems making occurrence of thrombosis or embolies into a risk (according to the orthopedic surgeon's judgement)
- Existing endoprosthesis at any other joint (e.g. hip or contralateral knee) to prevent infection of existing prosthesis
- History or presence of joint infection/inflammation
- Hypersensitivity to antibiotics
- Presence of systemic inflammatory disease, like rheumatoid arthritis

- Extra for **the GODIVA-bone substudy**: Inability to undergo a knee-MRI or knee-CT and DEXA according to the local enforced criteria in regular health care.

4.4 Sample size calculation

In the recently performed 'StWP' evaluation of KJD by ‘Zorg Instituut Nederland (ZiN)’ a non-inferiority limit for the 'crucial' endpoint of total WOMAC score at 2 years (the primary endpoint here) was defined at 15.

Assuming a ‘true’ difference in total WOMAC score of 12 points in favor of KP based on previous (pilot) data with an SD of 15 (14), 527 patients need to be recruited into each arm to obtain 90% power (2.5% one-sided significance) to demonstrate ‘non-inferiority’ (calculated using the power procedure in SAS 9.4). To account for missing data and loss to follow-up, we increase the sample size with ~15% and will include 600 patients per group.

Sample size considerations for the GODIVA-bone substudy: The response outcomes to use for the prediction models have an occurrence between ~30% and ~50%, indicating that with the 200 patients included (2/3 responder, i.e. 134 patients) we will have between 60 and 100 events for our analysis (between 40 and 67 for model development). Based on general rule of thumb, where at least 5-10 events per variable studies are needed we will have room for maximally 13 predictive parameters. To adhere to this, when needed, we will use data reduction techniques (e.g. principal component analysis or other feature reduction/selection techniques) or analysis techniques, suitable for sparse data, like penalized regression techniques to be defined in the SAP. For the secondary aim (explorative) we will relate changes in bone parameters to changes in pain (WOMAC pain) and cartilage tissue repair (radiographic joint space width increase) over a period of two years. The same parameters as explored in the predictive analysis as well as changes therein will be used as independent variables in this analysis.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

KP (total- or unicompartmental KP, at the discretion of the treating orthopaedic surgeon in consultation with the patient) is performed according to NOV guidelines as used in clinical practice.
KJD is performed according to the NOV recommendations for clinical care (see appendix S).

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable. Patients may use (pain) medication (which will be recorded) according to regular care NOV and participating institute guidelines/recommendations. If needed further surgical interventions (e.g. arthroplasty or revision for KJD and KP) in line with regular care, NOV and local guidelines will be performed (and registered).

6. INVESTIGATIONAL PRODUCT

Not applicable. As confirmed by the CCMO (email d.d. sept 8th 2021), this study does not fall within the scope of the medical device regulation.

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome of this randomized non-inferiority trial is the WOMAC total score at 2 years. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score (0-100; higher is better) is a combination of (sub scores for) pain, disabilities, and stiffness, all relevant to the patient, making it the preferred primary outcome for our study.
The WOMAC score is calculated based on the KOOS questionnaire (Appendix A), which is a freely available questionnaire (unlike the WOMAC questionnaire) and contains, the same questions as the WOMAC and questions for two additional domains function in daily living and function in sports and recreation. Therefore, WOMAC scores are often calculated based on this instrument. Contrary to the KOOS scores, a total score (based on the individual sub-scores) can be calculated for the WOMAC, which is not advised for the KOOS (see www.koos.nu).
Finally, the WOMAC total score is one of the 'crucial endpoints' as defined in the StWP process by ZiN to decide on reimbursement for this promising treatment in consultation with all stakeholders (such as the professional and patient associations).

8.1.2 Secondary study parameters/endpoints (if applicable)

- WOMAC sub-scores for pain, stiffness, and function (0-100)
- KOOS scores for Pain, Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec), and knee related Quality of life (QOL) (all scored on a 0-100 scale)
- SF36 physical component score and mental component score (0-100)
- NRS-pain (0-10)
- Patient Acceptable Symptom State
- NRS-satisfaction (0-10)
- EQ5D-5L for generic Quality of Life
- Pain medication (custom made questionnaire to assess the use of pain medication during the assessment period (last week) of the KOOS pain questionnaire)
- (serious) adverse events; including pin-tract infections based on a custom made CRF.
- Occurrence of surgical reinterventions (KP and revision arthroplasty procedures)
- Radiographic Joint space width (for KJD only) in millimetres using KIDA (Knee Images Digital Analysis; 15) as well as overall K-L grade from the same image.

See Appendix A – N

8.1.3 Tertiary study parameters

- Medical Consumption Questionnaire (MCQ; Appendix Q) and Productivity Cost Questionnaire (PCQ; Appendix R)
- Knee flexion (using a goniometer as measured during regular clinical visits; Appendix O)

Primary, secondary and tertiary outcomes include all outcomes relevant to and often used in (knee-) OA studies. This list of outcomes is also fully in line with the Standard Set of outcome measures and case-mix factors for monitoring, comparing, and improving health care for patients with clinically diagnosed hip or knee osteoarthritis (OA), developed with a focus on defining the outcomes that matter most to patients (developed by ICHOM (16)).

8.1.4 Other study parameters (if applicable)

General demographics such as age, gender, BMI as well as clinical parameters such as previous surgery (Appendix P) at the index knee and current indication for type of KP (TKP or UKP) will be evaluated. Some of these are well known prognostic factors for the prognosis of knee OA and/or effectiveness of KP or KJD treatment (16) and as such may act as treatment effect modifiers which will be explored.

The (limited) preference patients (Appendix H) participating in the study may have for one of the treatments will be measured and the effect on treatment effectiveness explored. OA severity (measured by the Charnley score, Appendix I) and patients general health (ASA classification, Appendix J) will also be measured as a descriptive variable as well as to make future matching of patients to patients from the Dutch national registration of orthopaedic implants (LROI) possible (outside the scope of this proposal).

Finally, the Pain-Detect Questionnaire (Appendix K) will be assessed at baseline to identify neuropathic components of a patients' pain, which may also be relevant with regard to patients prognosis and treatment effects.

For the GODIVA-bone substudy: Evaluation of imaging markers will be performed in three stages.

In the first stage, bone parameters will be scored, as scoring would be easily feasible to apply in clinical practice for the assessment of suitability for KD treatment. From radiographs, subchondral bone structure, and osteophytes will be scored automatically, which can be done with KOALA software (ImageBiopsyLab; [Jansen M et al. Osteoarthr Imag 2022;100018]). From DEXA scans, the T- and Z-score output

will be used [Ishii Y et al. Open Orthop J 2016;10,]. From CTs, subchondral bone density, cysts and osteophytes will be scored using the OACT scoring system [Gielis W et al. J Pers Med 2020;11,]. From MRI scans, bone marrow lesions (BMLs) and cysts will be scored with the WORMS scoring method [Roemer F et al. Osteoarthr Cartil 2016;24,].

In the second stage of the GODIVA-bone substudy, bone parameters will be measured as continuous parameters, which is more time consuming but results in more sensitive measures. From radiographs, subchondral bone density and osteophyte size will be measured using KIDA software [Marijnissen A et al. Osteoarthr Cartil 2008;16,; Jansen M et al. Osteoarthr Cartil 2021;29,]. Bone mineral density will be measured from DEXA scans [Lo G et al. Semin Arthritis Rheum 2018;48,]. Subchondral bone density, cortical bone thickness and osteophyte volume will be measured from CT scans [Mastbergen S et al. Osteoarthr Cartil 2022;30,]. BML and cyst volume will be measured from MRI scans [Roemer F et al. Osteoarthr Cartil 2010;18,].

In the third stage of the GODIVA-bone substudy, image classification machine learning models (like convolutional neural networks) will be used for all imaging types to classify (in our case predict) which patients will be clinical and/or structural responders. These models can be used restricted (i.e. the model can only look at bone) and unrestricted. Available baseline images will be divided in training, validation, and test sets, to develop and confirm results of machine learning algorithms. At present we have gained experience in this approach by ML using images of PsA patients [Arbabi S et al. 2022; ms in preparation]. Final algorithms can not only be used directly for prediction; looking at which parts of the images are most important for the ML model provides additional information on which (bone) sites and properties are important for clinical and/or structural response and thus allow the definition of new features or combined selection of features from imaging to use in an overall prediction model (see below).

For biochemical data we will use serum/plasma samples and urine samples. When all baseline samples are collected, the state-of-the-art selection of bone biomarkers at that time will be made, together with experts in the field (Nordic Bioscience), and analysed (within feasibility with respect to costs).

Where relevant these results will be integrated with the endpoint analyses of the GODIVA trial.

8.2 Randomisation, blinding and treatment allocation

After written informed consent has been obtained and patients fulfil the eligibility criteria they are randomised via the EDC system (Castor).
Randomisation will be performed centrally using blocked-randomisation (random block size) stratified by center and gender using the validated randomization unit from Castor (www.castoredc.com). This is an unblinded study.

8.3 Study procedures

The following study assessments will be performed according to the schedule below. See appendices B-P for questionnaires.

	Screening/ Baseline	Pre-surgery	Surg	Post-surgery							
Weeks/ months	-2m (max)		0	3w	6w	2m	5 m	8 m	12 m	24 m	ET
				+/- 1w	+/- 1w	+/- 2w	+/- 1m	+/- 1m	+/- 1m	+/- 2m	
Visits	**V0**			v1		v2	v3	v4	v5	**v6**	
General											
Informed consent	x										
In- and exclusion criteria	x										
Demographics/ characteristics	x										
Surgical medical history index knee	x										
Randomization		x									
Surgical treatment											
Knee prosthesis (KP) or Knee Joint Distraction (KJD) frame placement			x								
Removal KJD frame					x						
Questionnaires											
Pain Detect (neuropathic pain)	x										
KOOS (incl. pain medication)	x						x	x	x	x	
SF36	x								x	x	
EQ5D-5L	x			x		x	x	x	x	x	
NRS-Pain	x			x		x	x	x	x	x	
Patient Acceptable Symptom State	x						x		x	x	
NRS-Patient satisfaction							x		x	x	
Medical Consumption Quest. (MCQ)	x					x	x		x	x	
Productivity Cost Quest. (PCQ)	x					x	x		x	x	
Other											
Radiographic Joint space width (follow-up for KJD only) in mm **	x								x	x	
Adverse events/ additional surgical procedures *				*x*	*x*	*x*	*x*	*x*	*x*	*x*	
Knee flexion*	x			*x*	*x*	*x*	*x*	*x*	*x*	*x*	
Phone call											x
GODIVA-bone substudy#											
Informed consent substudy	x										
In- and exclusion criteria substudy	x										
Image and biochemical markers for bone ##		x								x	

* Adverse events / additional surgical procedures and knee flexion are specifically registered during regular care visits in a standardized way (continuous registration) so no study specific visits are planned for these measurements. Knee fexion is also measured at the baseline visit

** Radiographs of the knee (according to KIDA protocol) for follow-up will only be taken after KJD (baseline X-ray for both KJD and KP). Only the 24-month x-ray is extra compared to KJD treatment in regular care according to preliminary NOV recommendations. Visits depicted in bold are study-specific clinic visits.
# only for patients treated with KJD
only for patients participating in the GODIVA-bone substudy

1. At the study-specific baseline visit, after signing informed consent, in-and exclusion criteria will be formally checked. A radiograph of the knee is taken according to KIDA protocol (if a KIDA radiograph < 6 months is not available). This is in line with the KJD protocol for clinical practice recommended by the NOV (the Dutch orthopaedic society). If the patient is eligible, basic demographic and clinical information including the (limited) preference patients may have for any of the treatments is collected. In addition, questionnaires will be sent via email (via Castor EDC). When patients do not wish to receive digital questionnaires, they will receive paper versions by regular mail.
2. The patient will be randomized and will be informed about his/her allocated treatment (via phone or e-mail).
3. The patient will be invited for a pre-operative visit according to local clinical practice. During this visit, further details with respect to surgical and care practice (e.g. aesthesia) is provided in line with clinical practice in the respective centre. Surgery will be performed as soon as possible after this visit. Information about the techniques that are used for treatment (e.g uni- or total prosthesis and type of distraction device), will be documented in Castor.
4. Surgery will be performed according to local clinical practice.
5. The clinical checks after surgery will be performed in line with local clinical practice. Accoring to regular practice, patients treated with Knee prosthesis will visit the orthopaedic surgeon at ~6 and ~12 months after surgery for a clinical check. Patients treated with Knee Joint Distraction will visit the orthopaedic surgeon after ~3 weeks for a clinical check, at 6 weeks for removal of the distraction frame, and at ~6 months and at ~12 months after surgery for a clinical check. Although the clinic visits for check-up are not part of the study visits and follow regular care practice at the local center (and thus are not specifically depicted in above scheme), data on adverse events occurring will be specifically collected during the regular care visits in a standardized way (continuous registration, via standard notation in electronic health records and entered in Castor via EHR review). This is also the case for the standard measurement of knee flexion. Questionnaires will be sent to all participants via email (via Castor EDC) at 3 weeks and at 2, 5, 8, 12 and 24 months after surgery/start distraction period). At 12 and 24 months after surgery, only patients treated with joint distraction will be invited to come to the hospital for a radiograph of the knee (after 12 months is part of regular care according to NOV recommendations). At 24 month all patients will be contacted and asked if any additional surgical procedures of the knee have been performed or planned, which will be noted.

6. In case of early study termination, a phone call will be made to ask for the reason of termination and ask if any additional surgical procedures of the knee have been performed or planned.

For the GODIVA-bone substudy: Standard(ised) knee-MRI (single clinical time slot comprising 3 sequences), standard(ised) knee-CT, standard(ised) DEXA (according to the Imaging manual of the substudy), vena puncture for 2 times 7 cc blood and a urine sample will be collected at baseline and 2 years after treatment. Imaging and sampling will be performed as much as possible during the visits of the GODIVA study. Only for a limited number of patients extra visits may be needed.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Patients will then receive regular care. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable for the trial.

For the GODIVA-bone substudy: In case patients withdraw after informed consent for the substudy before the first pre-treatment data gathering, the subject is replaced ensuring the 200 patients baseline data-sets. As the change over two years is exploratory, subjects from which follow-up (at 2 years) data are missing are not replaced.

8.6 Follow-up of subjects withdrawn from treatment

As KP and KJD are interventions during a (reasonably) short period we do not expect withdrawal from treatment. In the unlikely event a patient does not undergo the treatment he/she was randomized to, he/she will remain followed according to the protocol. Note that this can be only one way, refusing KP will not result in KJD as this is not approved reimbursed standard of care. Reasons for deviations from the treatment protocol will be recorded and the patients will be accounted for in the analysis appropriately (ITT and in PP these patients will be excluded).

8.7 Premature termination of the study

We do not expect premature termination of the study to be necessary, as both treatments have been used (extensively) previously in studies and clinical practice and our study follows clinical practice.

The additional image and sample acquisition for the GODIVA-bone substudy is relatively simple and with that feasible and is not considered a reason for premature termination.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to KJD or KP. All adverse events reported spontaneously by the subject or observed by the investigator, or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor (UMCU) will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge

for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Exceptions to above SAE reporting to the accredited METC are the following expected, pre-determined SAEs (although these of course will be documented):

- a KP or revision surgery of the index knee within 2 years after (failure of) the KJD/KP treatment
- With respect to KJD, a pin tract infection for which the patient is treated temporarily with intravenous antibiotics

These SAEs will be reported in line listings, in annual progress reports.p

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

All AE and SAE will be monitored and treated according to standard of care and will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

Given the obvious advantages of preserving a patients' own knee, KJD needs to demonstrate 'non-inferiority' on the medium-long (2 year) term.
A full statistical analysis plan (SAP) will be in place prior to the analysis of trial data. All analyses and patient populations will be predefined in this SAP. Both intention-to-treat (ITT) and per protocol (PP) analyses have biases so neither can be regarded the 'gold standard' for non-inferiority trials but these approaches can make critical differences to the results of a trial (18). The trial will be analyzed and reported according to CONSORT extension for Non-Inferiority and Equivalence Randomized Trials (19).

The primary endpoint, the total WOMAC score at 2 years, will be compared between groups using (multivariable) random effects (mixed) modelling to account for the nested and longitudinal structure of the data over the 24 months follow-up. In case residuals of the model are not normally distributed , transformed scores will be used in the regression modelling. In this analysis time will be used as a categorical variable (5, 8, 12 and 24 months), and an interaction between time and the treatment-arm variable will also be included. A random intercept at patient level as well as at center level will be included. The stratification factors for randomization, center (using a random intercept) and gender, as well as a limited number of a priori defined prognostic factors (i.e. baseline WOMAC total score, age, BMI, and severity of cartilage damage) will be accounted for in this analysis used as fixed covariates. Baseline WOMAC score will be used as a continuous covariate (similar to the outcome variable), as well as age and severity of cartilage dame which can be regarded a reasonable assumption given the limited, expected range (in patients with age ≤ 65 and severe knee OA (K&L grade > 2)). As we expect that the effect of BMI may be non-linear, we will use BMI as a categorical variable using the CDC classification (BMI < 18.5, underweight; 18.5 to <25, healthy weight; BMI 25.0 to <30, overweight; BMI 30.0 to < 35 (max allowed in the study) obesity).

A random effect of time will also be tested in the model. The difference in mean total WOMAC score at 24 months between treatment groups will be estimated from this model with a 95% confidence interval (CI). The lower limit of this interval will be compared to the non-inferiority limit. If the lower limit of the confidence interval does not overlap the non-inferiority limit, KJD will be considered non-inferior. The non-inferiority limit is predefined

and accepted as 15 for the primary outcome (WOMAC total score) (See also at sample size calculation, 14).

The above analysis will be performed primarily on the per protocol (PP) population, i.e. patients that received their randomised treatment (and completed the 6 week distraction period for patients randomised to KJD only). The analysis will be repeated, for sensitivity reasons, for the ITT population defined as all patients who were randomized to one of the treatments.

A secondary analysis of the primary endpoint will be performed using (simple, multivariable) linear regression modelling, using only the 24 month WOMAC total scores. Multiple imputation will be used with > 10% missing data. This analysis will also be made the primary analysis when assumptions for the mixed model analysis do not seem to hold or convergence problems occur.

10.2 Secondary study parameter(s)

The analysis for continuous secondary outcomes follow the analysis strategy of the primary outcome. Binary, secondary outcomes will be compared using logistic multi-level regression analysis. The stratification factors for randomization (center and gender) will be used as (fixed) covariates in the analysis and the analysis will be adjusted by a limited number of a priori defined prognostic factors (e.g. baseline WOMAC total score, age, BMI, and severity of joint damage). Relative Risks (RR) with 95% confidence intervals will be estimated.
The upper limit (lower limit for response outcomes) of the confidence interval will be compared to the respective pre-defined non-inferiority limits to determine ‘non-inferiority’. An ITT and a PP analysis will be performed.
The number of complications will be reported as the frequency and percentage of events and frequency and percentage of patients experiencing events per (type of) complication. Additional arthroplasty procedures, specifically a primary knee prosthesis after KJD and revision surgery (e.g. total after hemi prosthesis) after a primary knee prosthesis will be described per group.
Radiographic assessment of joint space width, as an indicator of cartilage repair, over a two-year period will be reported descriptively in the KJD group. Differences from baseline (pre-treatment) will be tested with paired t-tests or Wilcoxon rank sum tests depending on the distribution of the data at 1 and 2 years follow-up.

Missing data will be minimised using centralised data acquisition for all participating centers coordinated from the UMC Utrecht with appropriate monitoring on data queries and will be imputed using multiple imputation by chained equations for the analyses.

10.3 Other study parameters

Quality adjusted life years will be calculated and described using means with 95%CI and direct and indirect costs will be calculated and described using medians and IQR, and also means with 95%CI based on bootstrapping separate per group. Differences will also be tested (using bootstrapping).

Modification of the treatment effect by (Age, gender, BMI, cartilage damage, and the presence of a neuropathic pain component) will be explored using state of the art methods in collaboration with the Julius Center. Subgroup effects for patients treated with a unicompartmental and total KP as initial treatment (or planned initial treatment when randomised to KJD) will be performed as well.

With respect to the GODIVA-bone substudy;

Development of prediction model: A multivariable prediction model will be developed to predict the response after KD treatment. Separate analyses for clinical success (defined as 15 points improvement in WOMAC pain), radiographic success (any increase in minimal JSW (>0 mm)) and success both clinically and radiographically will be performed. Also, more stringent cut-offs will be used e.g. based on the minimal detectable change. Model building will be performed stepwise starting with the predictive parameters that are more easily accessible in regular clinical practice (e.g. demographics and scores of bone parameters) as predictors, and thereafter the more demanding parameters (i.e. continuous scores, parameters derived from more sophisticated imaging modalities) are added. The total set of parameters to use as predictors in multivariable modelling will be decided based on initial findings (e.g. analysis during the third stage as described above), external findings from e.g. literature as well as clinical and biological expertise.

The modelling technique to use will be determined by experimentation, predictive performance, robustness, and ‘explainability’ of models and will be decided in discussion with clinicians, epidemiologists, data scientists and patients to ensure that the resulting models are statistically adequate and clinically useful.

All prediction models will be developed and externally validated (e.g. by using 2/3 of the data for development (including cross-validation for internal validation) and the remaining data as external validation data).

All data handling procedures and analyses to be performed, including the handling of missing data, specific features to be developed, and algorithms to use will be described in

a Statistical Analysis Plan (SAP) before ‘database lock’. This SAP will be finalized in cooperation with the methodologists from our department and from the Julius Center with which we cooperate in several other projects. Models will be developed and reported according to the TRIPOD criteria [Collins G et al. BMC Medicine 2015;13,].

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

When a patient visits the outpatient clinic and is considered for a KP and can also be considered for KJD, the orthopaedic surgeon will inform the patient briefly about the study and both treatment options. If the patient is interested to participate, an appointment with the investigator and/or research nurse is made (can be directly after/during the clinic visit, or by telephone call). Both information regarding the study and information related to both treatment options KP and KJD will be provided. All information is also provided in writing (Patient Information Form for the study and information regarding both treatment options). As local treatment procedures (logistical and other, e.g. pre-operative work-up, number of days admitted, provision of physiotherapy, etc.) can differ between centres according to local practice this will be communicated as such to patients by the respective orthopaedic surgeon/centre according to local practice as this may be relevant for decision making in this pragmatic study.

Patients will be given as much time to consider their participation in the trial as needed, with a minimum of 1 week. Thereafter, the patient is asked by phone (or e-mail) by the investigator/research nurse for her/his decision. In case patients do refuse participation, regular care (KP) follows. In case patients are willing to participate they are invited for a screening/baseline visit. At this visit informed consent is signed by both patient and investigator/ research nurse.

GODIVA-bone substudy:

During the informed consent procedure of the GODIVA study, patients will be asked to participate in the add-on GODIVA-bone study. An investigator or research nurse will contact (by phone, email, or face-to-face visit) the patient to provide the necessary information on the add-on GODIVA-bone study. Patients will be explained that it is only possible to participate when they are randomized to knee distraction treatment. Subsequently study information in writing will be provided/sent and patients will be contacted by the investigator or research nurse after at least one week to answer

possible questions and/or to obtain verbal consent for participation. At the screening / baseline visit informed consent for the add-on study will be signed by patients who are willing to participate and the research physician or research nurse. If patients are randomized to knee prosthesis, they will not be able to participate.The patients who are randomized to joint distraction treatment will be planned for imaging, before surgery will take place.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

The benefits and risks for the patients treated with KP are fully according to clinical practice. Patients should realize that in the Netherlands KJD is still not reimbursed and is only provided within the setting of the current clinical trial.

The benefit of a KP over KJD might be the swifter and slightly better clinical effect of treatment although at the expense of the original joint and with the higher risk of revision surgery later in life. The benefit of the KJD over a KP is that the original joint is preserved with the chance of postponing placement of a KP and decreasing the chance of revision surgery later in life, although with the burden of a 6-week distraction period with the chance of skin pin-tract infections, and possibly a slightly (non-clinically relevant) lesser clinical benefit.

In both arms, at 7 moments questionnaires must be filled out without the need of a clinic visit. At baseline for both treatments, and in case of KJD treatment additionally at 24 months a clinic visit takes place (the latter for a study specific x-ray) in addition to the typically 4 clinic visits performed in regular practice. In both arms a comparable number of knee radiographs is made in regular care and for KJD the 24 months study specific x-ray will be made.

In both arms the chance of failure is <5% in the first year after treatment. Failure can be due to multiple reasons, mostly persisting pain, leading to either revision surgery in case of a KP or placement of a first KP in case of KJD. Additionally, there is a chance of infection in both arms. In case of KJD these are primarily superficial skin pin tract infections, in generally successfully treatable with oral antibiotics. In both arms a small chance for deeper infections up to osteomyelitis are seen, needing i.v. antibiotics and/or nettoyage or even removal of the frame in case of KJD or early revision surgery in case of KP. Rehabilitation after the intervention(period) is similar for both treatment arms.

GODIVA-bone substudy: There is no direct benefit for the patient. Patients add to future well-balanced decision making by patient and surgeon together (shared decision-making) on whether to be treated with knee distraction or not, based on a scientifically justified chance for success of knee distraction treatment, is key for future implementation of knee distraction. Additionally, they will add to a more in-depth insight in the relationship between peri-articular bone changes and improvement in pain perception and cartilage repair, which may add to development and/or improvement of new and existing treatment strategies for knee osteoarthritis directed towards bone.
Minimal risks are related to imaging procedures including radiation exposure by CT and DEXA imaging, as well as vena puncture.
An indirect advantage is that for each patient a personalised feedback on the changes in bone parameters as a result of the treatment can be provided after end of the study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The Sponsor has an insurance by which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.
1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. Five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable. In case patients need an additional visit above the standard clinical and GODIVA trial related visits, travel costs will be reimbursed.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The UMC Utrecht will be responsible for the management and coordination of the trial. Data will be collected and stored pseudonymised in a web-based EDC system: Castor.

The subject-ID number consists of a number indicating the study, followed by a number for the participating center at which the patient is included, followed by a number indicating the subject. The key to the code is safely kept by the local coordinating investigator in each participating center. Data will be stored for 15 years.

For more information on the handling and storage of data please see the 'Data Management Protocol' that has been approved by a data-manager of the UMCU.

12.2 Monitoring and Quality Assurance

The study will be monitored by a central monitor of the UMCU, according to the monitoring plan in line with the guidelines of the NFU.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

Non-substantial amendments (e.g. typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation) will not be notified to the accredited METC, but will be recorded and filed by the Sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The principal investigator is also the sponsor of this study and will follow the basic principles of the CCMO's position on the disclosure/publication of research results as described in the 'statement on publication policy' on the website of the CCMO.

13. STRUCTURED RISK ANALYSIS

Not applicable

13.1 Potential issues of concern

Not applicable for any of the items

a. Level of knowledge about mechanism of action
b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism
c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
d. Selectivity of the mechanism to target tissue in animals and/or human beings
e. Analysis of potential effect
f. Pharmacokinetic considerations
g. Study population
h. Interaction with other products
i. Predictability of effect
j. Can effects be managed?

13.2 Synthesis

Not applicable

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15. APPENDICES