

Clinical Trial Protocol

Clinical Trial Protocol Number	EMR700692_006
Title	A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to investigate the efficacy and safety of different intra-articular (i.a.) dosages of sprifermin in subjects with primary osteoarthritis of the knee (FORWARD)
Trial Phase	II
IND Number	CCI [REDACTED]
EudraCT Number	2011-003059-20
Coordinating Investigator	PPD [REDACTED]
Sponsor	Merck KGaA Frankfurter Strasse 250, 64293 Darmstadt, Germany <i>(for the USA)</i> EMD Serono, Inc. One Technology Place, Rockland, MA 02370 USA Medical Responsible: PPD [REDACTED] EMD Serono, Inc. One Technology Place, Rockland, MA 02370, USA
Clinical Trial Protocol Version	05 Mar 2013/Version 4.0 (including Amendments 1 and 2)
Replaces Clinical Trial Protocol Version	13 Oct 2011/Version 3.0
Current Clinical Trial Protocol Amendment	Amendment No. 2 (Global), 05 Mar 2013

[REDACTED]

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Previous Protocol Amendments

- Amendment No. 1 (Non-substantial), 13 Oct 2011 (Global)

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

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Sprifermin
EMR700692_006

Phase II Trial of Sprifermin in Knee OA

Coordinating Investigator:

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

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Principal Investigator Signature

Trial Title A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to investigate the efficacy and safety of different intra-articular (i.a.) dosages of sprifermin in subjects with primary osteoarthritis of the knee (FORWARD) (EMR700692_006)

EudraCT Number 2011-003059-20

Clinical Trial Protocol Version/Date 05 Mar 2013/ Version 4.0 (including Amendments 1 and 2)

Center Number

Principal Investigator

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.
- I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

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List of Abbreviations

AE	Adverse event
AIR	Acute inflammatory reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BUN	Blood urea nitrogen
CFR	(United States) Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
COMP	Cartilage oligomeric matrix protein
coxib	COX-2 selective inhibitor
CRF	Case Report Form
CS846	Chondroitin sulfate epitope 846
CTX-II	C-telopeptide cross-linking of type II collagen
DBPC	Double-blind placebo-controlled
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram
EEA	European Economic Area
EF	Extended follow-up
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate

EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European clinical trials database)
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGF-18	Fibroblast growth factor-18
FGFR	Fibroblast growth factor receptor
FIM	First-in-man
FORWARD	FGF-18 Osteoarthritis Randomized trial With Administration of Repeated Doses
GBS	Global Biostatistics (department)
GCDU	Global Clinical Development Unit
GCP	Good Clinical Practice
GDS	Global Drug Safety (department)
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
i.a.	Intra-articular(ly)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICOAP	Measure of Intermittent and Constant Osteoarthritis Pain
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	Interleukin

IL-1ra	Interleukin-1 receptor antagonist
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention-to-Treat
IVRS	Interactive Voice Response System
JSW	Joint space width
KOOS	Knee Injury and Osteoarthritis Outcome Score
KOOS QOL	Knee Injury and Osteoarthritis Outcome Score quality of life subscale
LFTC	Lateral femorotibial compartment
LLOQ	Lower limit of quantitation
mcg	Microgram(s)
MedDRA	Medical Dictionary for Regulatory Activities
MFTC	Medial femorotibial compartment
mITT	Modified Intention-to-Treat
MOP	Manual of Operations
MOS SF-36	Medical Outcomes Study Short Form-36 General Health Survey
MRI	Magnetic resonance imaging
NCD	Non-Clinical Development (department)
N.B.	Nota bene (please note)
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OAI	Osteoarthritis Initiative

OARSI	Osteoarthritis Research Society International
OMERACT-OARSI	Outcome Measures in Rheumatology – Osteoarthritis Research Society International (responder criteria)
PD	Pharmacodynamic(s)
PGA	Patient’s Global Assessment
PGIC	Patient Global Impression of Change
PGt	Pharmacogenetics
PIINP	II form of the propeptides from the N-terminus processed type II collagen
PIICP	Propeptides from the C-terminus processed type II collagen
PK	Pharmacokinetic(s)
POC	Proof of concept
PP	Per Protocol
PRO	Patient Reported Outcome
QOL	Quality of life
QTc	Corrected electrocardiogram QT interval
RF	Rheumatoid factor
rhFGF-18	Recombinant human fibroblast growth factor 18
SAE	Serious Adverse Event
SF	Synovial fluid
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
ULN	Upper limit of normal (range)
VAS	Visual analogue scale
W	Week

WBC	White blood cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole Organ Magnetic Resonance Imaging Score

1 Synopsis

Trial title	A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to investigate the efficacy and safety of different intra-articular (i.a.) dosages of sprifermin in subjects with primary osteoarthritis of the knee (FORWARD)
Trial number	EMR700692_006
EudraCT number	2011-003059-20
Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany <i>(for the United States of America)</i> EMD Serono, Inc. One Technology Place, Rockland, MA 02370 USA
Phase	II
Trial under IND	<input checked="" type="checkbox"/> yes <input type="checkbox"/> no
FDA “covered trial”	<input checked="" type="checkbox"/> yes <input type="checkbox"/> no
Trial centers/countries	Approximately 10 to 15 trial sites located in Europe, the United States, and possibly other geographical regions
Planned trial period (first enrollment-last subject out)	Aug 2013 (first subject’s first visit) to Aug 2019 (last visit of follow-up phase)
Trial objectives	Primary: To evaluate structural changes in cartilage thickness in the total femorotibial joint of the target knee in terms of imaging by magnetic resonance imaging (MRI) Secondary: <ul style="list-style-type: none"> • To evaluate different dose regimens of sprifermin • To evaluate changes in symptoms of osteoarthritis (OA) • To evaluate changes in structure in terms of imaging by X-ray

	<ul style="list-style-type: none"> • To evaluate other changes in cartilage morphology in terms of imaging by MRI (sub-regions) • To evaluate changes in physical functioning • To evaluate the safety of sprifermin • To evaluate the pharmacokinetics (PK) of sprifermin in serum and in synovial fluid following i.a. injection <p>Exploratory:</p> <ul style="list-style-type: none"> • To evaluate responder criteria in symptoms • To explore treatment effect on OA pain and other patient-reported outcomes (PROs) • To evaluate changes in quality of life (QOL) • To explore treatment effect on the knee joint and bone structures by MRI • To evaluate long-term treatment effects • To explore the relationship between the change over time in synovial, serum, and urine biomarkers (e.g., cartilage and bone tissue turnover markers, inflammation markers) and the response to the drug • To evaluate potential associations of biomarkers (e.g., genetic variations or protein biomarkers measured at baseline) with drug response, and/or disease severity or disease progression • To explore the relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time, by means of modeling
<p>Trial design and plan</p>	<p>The trial consists of a screening period, a double-blind placebo-controlled (DBPC) treatment phase, and an extended follow-up phase.</p> <p>Subject eligibility for the trial will be determined during the screening period based on clinical and radiographic criteria, in addition to responses to pain questionnaires after withdrawal of analgesic medications.</p> <p>In the 2-year DBPC treatment phase, subjects will be randomized in equal allocation to one of 5 treatment groups (see below).</p> <p>All subjects will receive 4 cycles of treatment with the Investigational Medicinal Product (IMP; sprifermin or</p>

	<p>matching placebo) at intervals of 6 months. Each cycle will consist of 3 once-weekly i.a. injections over a period of 3 consecutive weeks.</p> <p>Efficacy assessments will include MRI and X-ray of the target knee, the WOMAC, the 20-meter walk test, and a Patient’s Global Assessment of disease impact (PGA). The Patient Global Impression of Change (PGIC), the Knee Injury and Osteoarthritis Outcome Score (KOOS) QOL subscale (KOOS QOL), the KOOS Symptom Index, the Medical Outcomes Study Short Form-36 General Health Survey (MOS SF-36), assessment of pain (on a numerical rating scale [NRS]) in the target and contralateral knee, identification of pain in other joints, and the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire will be assessed as exploratory outcomes.</p> <p>Adverse events (AEs), concomitant medications, and procedures will be monitored throughout the trial.</p> <p>See below for details of safety and other assessments.</p> <p>The 3-year extended follow-up phase will include periodic assessment of the WOMAC, NRS pain score in the target and contralateral knee, PGA, PGIC, KOOS QOL and Symptom Index, MOS SF-36, 20-meter walk test, identification of pain in other joints, and ICOAP as well as safety assessments. MRI and X-ray will be performed at yearly intervals.</p> <p>It is planned to perform the statistical analysis in two steps, as described in Section 8.5.1: results from the DBPC treatment phase will be analyzed and reported at the end of this phase, and long-term follow-up data will be analyzed and reported separately. MRI readers, Investigators, and subjects will remain blinded during the extended follow-up phase.</p>
<p>Planned number of subjects</p>	<p>545 subjects will be randomized.</p> <p>Approximately 10 to 15 trial sites in Europe, the United States, and possibly other geographical regions will participate in the trial.</p>
<p>Schedule of visits and assessments</p>	<p>The screening period will comprise a period of 4 to 42 days during which a subject’s eligibility will be</p>

	<p>determined, beginning at signature of the ICF. During the screening visits, eligibility will be assessed and the target knee will be defined. At the baseline visit, eligibility will be confirmed, randomization will occur, and the first IMP injection will be given (Week 0/Visit 2). The last of the four cycles of 3 injections of IMP will be given on Week 78/Visit 17, and the last dose of IMP is scheduled to be administered at Week 80/Visit 19.</p> <p>Trial visits during the two-year DBPC treatment phase will take place at Weeks 0 (randomization and first IMP injection), 1, 2, 3, 12, 26, 27, 28, 29, 38, 52, 53, 54, 55, 64, 78, 79, 80, 81, 90, and 104.</p> <p>Major efficacy assessments will take place on the first day of each treatment cycle and then at the end of the DBPC treatment phase (Week 104/Visit 22).</p> <p>Minor efficacy assessments will take place 9 weeks after each treatment cycle.</p> <p>AEs and concomitant medications will be reviewed and vital signs will be measured at all trial visits.</p> <p>Trial assessments during the 3-year extended follow-up phase will take place at 6-month intervals from Week 104/Visit 22 through Week 260/Visit 28.</p>
<p>Diagnosis and main inclusion and exclusion criteria</p>	<p>The trial will enroll adult subjects of either sex with primary femorotibial osteoarthritis according to American College of Rheumatology (ACR) clinical and radiographic criteria who have Kellgren-Lawrence grades of 2 or 3 and a minimum joint space width (JSW) of ≥ 2.5 mm in the medial compartment.</p> <p>Subjects must have pain in the target knee on most days and/or require symptomatic treatment of knee pain with paracetamol (acetaminophen), systemic non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 selective inhibitor (coxibs), or tramadol on most days of the previous month, and must have both:</p> <ul style="list-style-type: none">• A history of pain due to OA in the target knee for at least 6 months, and• Pain score for the target knee of 4 to 9 points in response to Question 1 of the WOMAC pain index (“how much pain have you had [in the target knee,

	<p>over the past 48 hours] when walking on a flat surface?") at screening and baseline, after washout of at least 5-half-lives of analgesic medication(s): acetaminophen, topical or oral systemic NSAIDS, coxibs, opioids, and/or tramadol.</p> <p>Women of childbearing potential must use a form of contraception with a failure rate of less than 1% per year throughout the trial.</p> <p>Main exclusion criteria are malalignment of > 5 degrees in the femorotibial axis of the target knee, clinical signs of inflammation (i.e., redness) in the target knee, i.a. administration of corticosteroids or hyaluronic acid into either knee within 6 months before screening, any plan for knee surgery (affecting either the target or the contralateral knee) within the next two years, concomitant conditions or treatments deemed to be incompatible with trial participation, contraindications to MRI scanning (including inability to fit in the scanner or knee coil), pregnancy or breastfeeding, participation in another clinical trial within the past 30 days, and legal incapacity or limited legal capacity.</p> <p>Full lists of inclusion and exclusion criteria are presented in Sections 5.3.1 and 5.3.2, respectively.</p> <p>Written informed consent must be obtained prior to any trial-related activity.</p>
<p>Investigational Medicinal Product: dose/mode of administration/ dosing schedule</p>	<p>Sprifermin (rhFGF-18) 30 mcg or 100 mcg, administered intra-articularly.</p> <p>Subjects will receive 4 cycles of treatment (each consisting of 3 once-weekly i.a. injections over 3 consecutive weeks) at intervals of 6 months.</p> <p>Subjects will be randomized in equal allocation to one of 5 treatment groups:</p> <ul style="list-style-type: none">• 4 cycles of sprifermin (100 mcg per injection)• 2 cycles of sprifermin (100 mcg per injection) alternating with 2 cycles of placebo• 4 cycles of sprifermin (30 mcg per injection)• 2 cycles of sprifermin (30 mcg per injection) alternating with 2 cycles of placebo• 4 cycles of placebo (see below)

Reference therapy: dose/mode of administration/dosing schedule	Placebo to match sprifermin, administered i.a. (see treatment regimen described above for sprifermin)
Planned treatment duration per subject	2 years
Primary endpoint	Change from baseline in cartilage thickness in the total femorotibial joint as evaluated by MRI at 2 years
Secondary endpoints	<ul style="list-style-type: none"> • Changes from baseline in the WOMAC total score and in the WOMAC pain, function, and stiffness index scores over 2 years • Change from baseline in the 20-meter walk test over 2 years • Change from baseline in the PGA over 2 years • Change from baseline in minimal joint space width in the medial and lateral compartments as evaluated by X-ray over 2 years • Change from baseline in cartilage thickness in the medial and lateral compartments as well as in the total femorotibial joint over 2 years • Change from baseline in cartilage volume in the medial and lateral compartments as well as in the total femorotibial joint over 2 years • Synovial fluid levels of sprifermin/FGF-18 • Serum levels of sprifermin/FGF-18
Safety endpoints	<ul style="list-style-type: none"> • Nature, incidence and severity of local and systemic AEs • Incidence of acute inflammatory reactions (AIRs), defined as increase of pain by 30 mm on a 100 mm visual analogue scale (VAS) and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection (see Section 7.4.1.1) • Changes in laboratory safety parameters, vital signs, 12-lead electrocardiogram (ECG) parameters, weight, and physical examinations • Incidence of surgical interventions in the target knee (including any surgical revision, cartilage removal, or any other type of surgical intervention). • Occurrence of binding and neutralizing antibodies to sprifermin/FGF-18

<p>Exploratory endpoints</p>	<ul style="list-style-type: none">• Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate (1) at 2 years• PGIC over 2 years• Changes from baseline in the scores of the KOOS QOL and the MOS SF-36 questionnaire over 2 years• Change from baseline in KOOS Symptom Index over 2 years• Change from baseline in NRS pain score in the target and contralateral knee over 2 years using an 11-point NRS• Change from baseline in presence of pain in other joints over 2 years• Change from baseline in ICOAP scores over 2 years• Change over time in structural as well as compositional parameters of the knee joint (e.g., synovium, menisci, bone, and other structures) as evaluated by MRI• Change from baseline in serum, urine, and synovial markers associated with administration of the compound• Baseline protein markers and/or genetic markers associated with response to treatment or disease progression (response assessed by MRI and/or questionnaire)• Changes in MRI outcomes, WOMAC scores, 20-meter walk test, PGA, PGIC, JSW, OMERACT-OARSI responder rate, KOOS QOL, KOOS Symptom Index, MOS SF-36, NRS pain score in the target and contralateral knee, presence of pain in other joints, ICOAP, safety laboratory values, and vital signs over the extended follow-up period and nature, incidence and severity of local and systemic AEs during the extended follow-up period (to be summarized descriptively)• Relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time
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Pharmacokinetics	Levels of sprifermin/FGF-18 will be measured in serum and synovial fluid for pharmacokinetic (PK) assessment
Other assessments	<p>Subject diary information about maximum levels of target knee pain and presence or absence of target knee swelling will be used to identify potential acute inflammatory reactions to the IMP.</p> <p>Exploratory pharmacogenetic (PGt) analyses will be performed for subjects who provide separate informed consent.</p>
Statistical methods (includes sample size calculation)	<p>Sample Size Calculation</p> <p>The number of 545 randomized subjects has been calculated to provide 90% power to detect a dose relationship as well as an overall treatment effect in the change from baseline in cartilage thickness in the total femorotibial joint at 2 years, assuming a discontinuation rate of 30% at that time. The study is also adequately powered to detect significant difference in at least one active treatment group and the placebo group for a secondary WOMAC endpoint such as the pain, function or total WOMAC score.</p> <p>Statistical Methodology</p> <p>The treatment effect on the primary endpoint will be assessed through dose-ranging using a repeated measurement analysis of variance (ANOVA, using PROC MIXED in SAS) on absolute change from baseline, including the baseline value, the treatment group, the time, and the country as factors and treatment by time as interaction.</p> <p>The primary efficacy analysis will consist of testing the linear dose relationship and the overall treatment effect at 2 years. The significance level will be set at 5% two-sided for both tests.</p> <p>Pairwise comparisons (sprifermin versus placebo, and between sprifermin dose and regimen groups) will be performed within the context of this modeling framework. For each pairwise comparison, the difference between treatments and the corresponding 95% confidence interval (CI) and p-value will be presented.</p>

	<p>The same ANOVA model used for the primary endpoint will be used to assess the treatment effect on continuous secondary endpoints such as MRI endpoints, WOMAC endpoints (total, pain, function, and stiffness scores), and X-ray endpoints at each time point and over time.</p> <p>Logistic regression will be used to assess the treatment effect on the binary efficacy endpoints such as the OMERACT-OARSI responder rate. Point estimates for each pairwise comparison and corresponding 95% CIs and p-values will be provided.</p>
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2 Sponsor, Investigators and Trial Administrative Structure

Sponsor

For countries other than the United States of America, the Sponsor of this trial is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

For the United States of America, the Sponsor of this trial is EMD Serono Inc. (One Technology Place, Rockland, MA 02370, USA).

Sponsor Responsibilities

The sponsor will be responsible for overseeing all aspects of the study.

External Service Providers

External service providers will be responsible for trial management, including central randomization and central laboratory analyses. Magnetic resonance imaging (MRI) and X-ray imaging data will also be acquired and read centrally. Details regarding the vendors involved and the responsibilities of each will be described in the MOP.

Investigators and Trial Sites

Overall, approximately 10 to 15 trial sites located in Europe, the United States, and possibly other geographical regions will contribute to this trial.

It is estimated that 2 of the enrolling sites will be located in the United States.

Coordinating Investigator

The Coordinating Investigator for this trial is PPD

(contact information is provided on the title page of this clinical trial protocol).

The Coordinating Investigator will serve as a representative of the trial Investigators in decisions and discussions regarding this trial (see International Conference on Harmonization Topic E6, Good Clinical Practice (ICH GCP), 1.19), providing expert medical input and advice relating to trial design and execution and being responsible for the review and sign-off of the clinical trial report on behalf of all Investigators.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be constituted and will perform periodic reviews to evaluate the safety of the subjects participating in the trial on an ongoing basis. Detailed description of the safety monitoring will be specified in a dedicated IDMC charter.

Trial Administrative Structure

Details of the trial's administrative structure are presented in the trial Manual of Operations (MOP).

3 Background Information

Osteoarthritis (OA) is an ever-increasing health problem in both industrialized nations and developing countries (2). The risk factors contributing to this epidemic are increasing body weight, lack of exercise, and the aging of a significant proportion of the population (3),(4),(5). The increasing number of individuals being affected by degenerative joint disease also translates into a significant financial burden on the health care system (6).

Despite the variety of treatment modalities available, no existing pharmacological treatments can influence OA disease progression or outcome. Consequently, there is considerable interest in the development of disease-modifying OA drugs.

Sprifermin is a truncated recombinant form of human fibroblast growth factor-18 (FGF-18). Endogenous human FGF-18 is a protein expressed by chondrocytes of articular cartilage which has been identified as a trophic factor for mature chondrocytes. In cell culture experiments, FGF-18 was shown to induce proliferation of articular chondrocytes and to stimulate synthesis of extracellular matrix (7). Furthermore, in an animal experiment, FGF-18 induced dose-dependent increases of cartilage thickness of the tibial plateau in rats after they had been subjected to meniscal injury. Both reductions in the cartilage degeneration scores and generation of new cartilage were seen in the treated animals (8).

Human FGF-18 is a 20-kilodalton secreted protein expressed by cells including chondrocytes and osteoblasts (9),(10). FGF-18 increases chondrocyte proliferation/differentiation and cartilage deposition and induces osteoblast differentiation, leading to bone remodeling effects (e.g., closure of growth plates) (7),(8),(10),(11),(12). FGF-18 is required for normal development, as homozygous knockout mice die shortly after birth (13),(14). Their phenotype includes skeletal defects.

Cell surface receptors for FGF-18 have been identified. Upon ligand binding mediated by heparin/heparin sulfate-containing proteoglycans, high-affinity fibroblast growth factor receptors (FGFR) 3c, 4, and 2c transduce intracellular signaling via tyrosine-kinase activity (15). FGFR3c, FGFR4, and FGFR2c are naturally expressed on chondrocytes of articular cartilage, as demonstrated by in situ hybridization (14),(15). FGF-18 has been shown to signal through FGFR3 to promote mesenchymal cell differentiation (chondrogenesis) and production of the cartilage matrix, leading to repair and reconstruction of a variety of cartilaginous tissues (7).

Sprifermin (recombinant human FGF-18; rhFGF-18; formerly known as AS902330) produced by Merck Serono is a truncated, non-glycosylated form of FGF-18, containing 170 amino acids. Sprifermin increases chondrocyte proliferation/differentiation and cartilage deposition, potentially leading to repair and reconstruction of a variety of cartilaginous tissues.

Unlike other members of the fibroblast growth factor (FGF) family, FGF-18 is not a general growth mediator but exhibits its effects specifically on chondrocytes (proliferation) and osteoblasts (differentiation). Nonetheless, significant systemic exposure to sprifermin may result in unacceptable side effects such as general cartilage and bone growth. Therefore, in order to

minimize systemic exposure and to limit the trophic effect of sprifermin to intra-articular cartilage, intra-articular (i.a.) injection will be used.

Nonclinical Data

Nonclinical studies performed with sprifermin are described in the sprifermin Investigator's Brochure (IB).

Clinical Data

Clinical trials performed to date with sprifermin are described in the sprifermin IB. To date, two Phase I trials of sprifermin in subjects with OA of the knee have been completed.

The randomized, double-blind, placebo-controlled multicenter first-in-man (FIM) trial 27575 included 73 subjects with OA in the femorotibial compartments of the knee who were candidates for total knee replacement. Subjects were randomized to receive i.a. injections of sprifermin at dosages of 3 mcg, 10 mcg, 30 mcg, 100 mcg, and 300 mcg or placebo in either single-dose or multiple-dose regimens. Multiple-dose regimens consisted of one treatment cycle of three injections given once weekly over a period of three weeks. Twenty-three subjects who received single-dose regimens and 26 subjects who received multiple-dose regimens underwent total knee replacement within a period of three months after completion of treatment. When the cartilage tissue specimens of the resected knees were examined by pathologists, specimens from subjects who had been exposed to dosages of 10 to 300 mcg sprifermin showed a trend to lower Mankin scores and higher Young modulus, both indicating an improvement of cartilage morphology, compared to subjects who received placebo. These effects were more pronounced in the multiple-dose groups. Furthermore, sprifermin had a favorable safety profile and was well tolerated in this trial.

The randomized, double-blind, placebo-controlled, multicenter proof-of-concept (POC) trial 28980 included 192 subjects with primary knee OA and Kellgren-Lawrence grade 2 or 3 who were not candidates for knee replacement. Subjects were randomized into groups receiving either placebo or three dosages of sprifermin (10 mcg, 30 mcg or 100 mcg) in either single-dose or multiple-dose regimens. Multiple-dose regimens involved two treatment cycles given 3 months apart.

A dose-dependent anabolic effect was seen on total cartilage volume and thickness as measured by MRI. The effect on structure was more pronounced in the lateral as compared to the medial compartment; statistical significance was not reached for the primary endpoint of change from baseline in cartilage thickness in the central medial femorotibial compartment. A significant dose-dependent effect was also seen for JSW, particularly in the lateral compartment, with the highest dose actually reversing joint space narrowing.

No local tolerability or systemic safety concerns were identified. One SAE was considered potentially treatment-related: bacterial arthritis in a subject who had received placebo. Subjects who received active treatment appeared to have slightly more acute inflammatory reactions (AIRs; defined as increase of pain by 30 mm on a 100-mm visual analogue scale (VAS) associated with a self-reported synovial fluid effusion within 3 days following i.a. injection) in

the treated knee; however, no dose-response relationship was evident. For additional updated clinical safety data on sprifermin, refer to the Investigator's Brochure.

In terms of modification of symptoms, WOMAC total score improved over the 12-month period in all groups, including placebo. The improvement of symptoms was most pronounced in the placebo group, while sprifermin-treated subjects experienced less symptom relief. This unexpected result was also seen for the WOMAC pain and function index scores and requires further investigation.

Rationale for the Present Trial

Sprifermin is a completely novel compound in the field of degenerative joint disease and it may be the first disease-modifying drug to become available to patients with OA.

Based on the results described above, this phase II trial is proposed to assess the dose-response-relationship of sprifermin in subjects with knee OA of Kellgren-Lawrence grades 2 and 3. The trial design is presented in Section 5.1; rationales for choices of trial design, subject population, dose regimen, and trial assessments are presented in Section 5.2, and the reasoning behind the choice of planned sample size is presented in Section 8.1.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, GCP) and the applicable regulatory requirements.

If the trial is positive, it will provide data on an optimized dose and dosing schedule of sprifermin, i.e., a dose and dosing schedule of the drug that will exert a disease-modifying action (i.e., both modification of structure and improvement of symptoms).

Currently very little is known about how modification of structure is linked to change in symptoms (i.e., perception of pain and function by the subject). This trial will also help to understand how change in cartilage structure correlates with change in symptoms.

To date, a total of 265 subjects have been included in the FIM and the POC trials using i.a. administration. All systemic levels of sprifermin/FGF-18 measured to date have been below the lower limit of quantitation (LLOQ), and no local or systemic safety issues have emerged. No systemic antibodies to sprifermin/FGF-18 have been detected, except in 3 subjects who already tested positive for binding antibodies at baseline. There may be a slightly higher incidence of AIRs in the target knee with dosages of 300 mcg sprifermin; however, the 300 mcg dosage will not be used in this trial. Considering all clinical and non-clinical experience, sprifermin can be regarded as having a favorable safety profile.

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date, the conduct of the trial is considered justifiable using the doses and dosage regimen of the Investigational Medicinal Product (IMP) as specified in this clinical trial protocol.

4 Trial Objectives

The trial's objectives are as follows.

Primary

- To evaluate structural changes in cartilage thickness in the total femorotibial joint of the target knee in terms of imaging by MRI

Secondary

- To evaluate different dose regimens of sprifermin
- To evaluate changes in symptoms of OA
- To evaluate changes in structure in terms of imaging by X-ray
- To evaluate other changes in cartilage morphology in terms of imaging by MRI (sub-regions)
- To evaluate changes in physical functioning
- To evaluate the safety of sprifermin
- To evaluate the PK of sprifermin in serum and in synovial fluid following i.a. injection

Exploratory

- To evaluate responder criteria in symptoms
- To explore treatment effect on OA pain and other patient-reported outcomes (PROs)
- To evaluate changes in quality of life (QOL)
- To explore the treatment effect on the knee joint and bone structures by MRI
- To evaluate long-term treatment effects
- To explore the relationship between the change over time in synovial, serum and urine biomarkers (e.g., cartilage and bone tissue turnover markers, inflammation markers) and the response to the drug
- To evaluate potential associations of biomarkers (e.g., genetic variations or protein biomarkers measured at baseline) with drug response and/or disease severity or disease progression
- To explore the relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time, by means of modeling

5 Investigational Plan

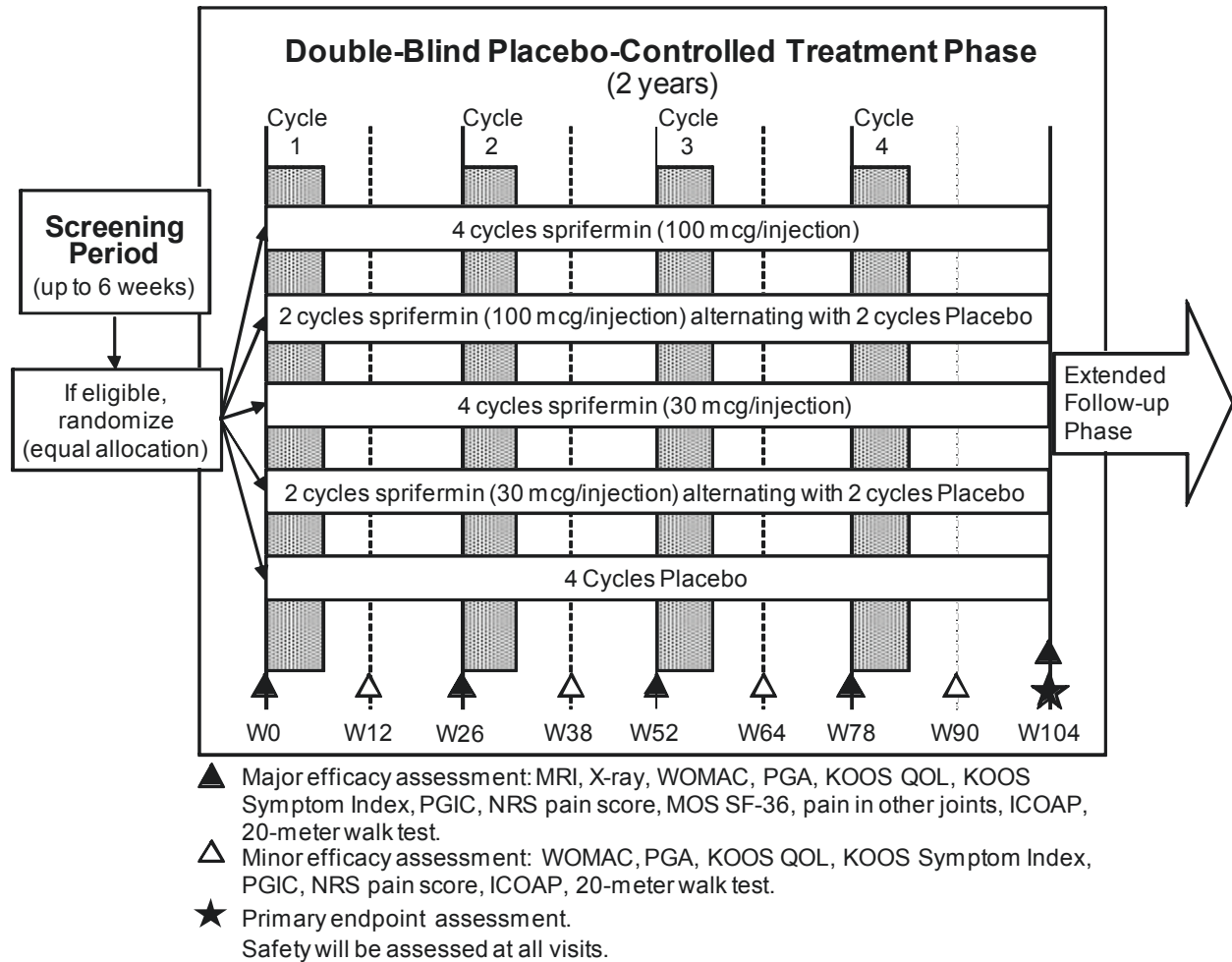
5.1 Overall Trial Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase II trial of sprifermin administered i.a. in subjects with primary OA of the knee and Kellgren-Lawrence grade 2 or 3.

The trial will randomize approximately 545 subjects (109 per treatment group); sample size calculations are described in Section 8.1.

The trial consists of a screening period lasting up to 42 days, a 2-year (104-week) double-blind placebo-controlled (DBPC) treatment phase, which will start at randomization (Week 0/Visit 2), and a 3-year extended follow-up phase (see [Figure 1](#) and [Figure 2](#)).

Figure 1 Trial Schema: Screening and DBPC Treatment Phases



Abbreviations: W: Week; MRI: magnetic resonance imaging; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: Patient's Global Assessment; KOOS QOL: Knee Injury and Osteoarthritis Outcome Score quality of life subscale; KOOS Symptom Index: Knee Injury and Osteoarthritis Outcome Score symptom index subscale; PGIC: Patient's Global Impression of Change; NRS pain score: numerical rating scale pain score; MOS SF-36: Medical Outcomes Study Short Form-36 General Health Survey; ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain.

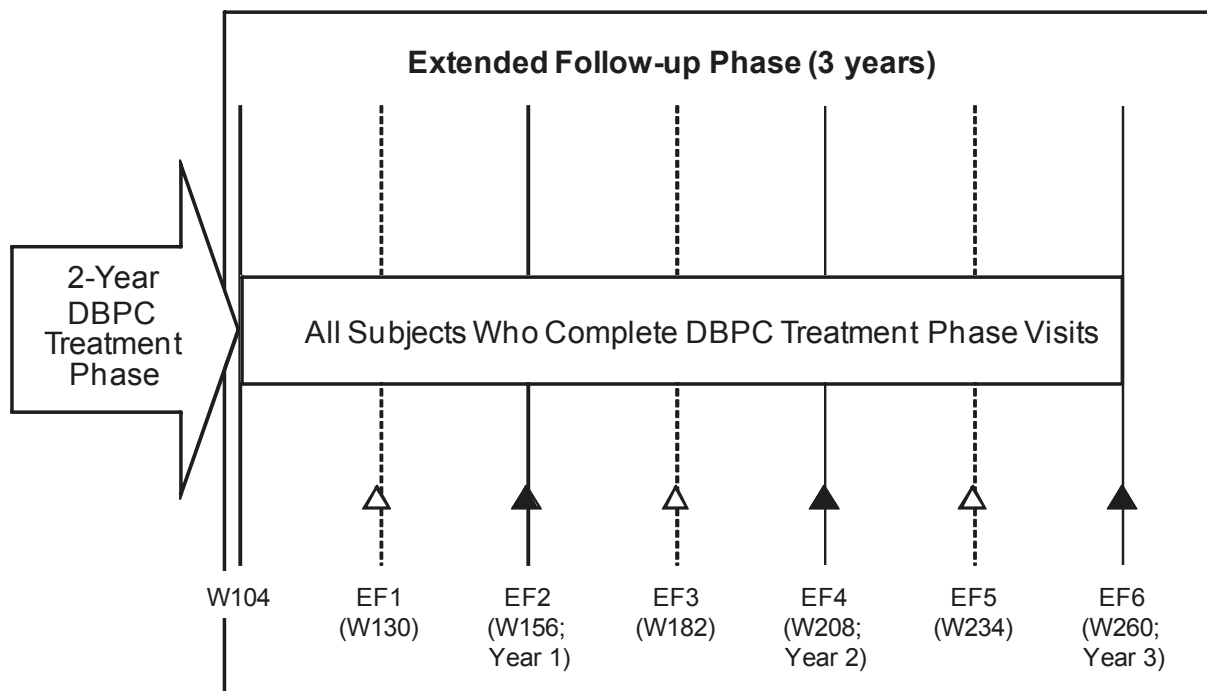
Each treatment cycle consists of one i.a. injection per week for 3 consecutive weeks.

DBPC treatment phase visits will occur at Weeks 0 (randomization and first IMP injection), 1, 2, 3, 12, 26, 27, 28, 29, 38, 52, 53, 54, 55, 64, 78, 79, 80, 81, 90, and 104.

Pain medications must be withheld for at least 5 half-lives before a visit involving completion of the WOMAC.

Adverse events, concomitant medications, and concomitant procedures (including concomitant surgical procedures on the target knee) will be monitored throughout the trial. Time points for safety, laboratory, PK, and biomarker assessments are shown in [Appendix E](#).

Figure 2 Trial Schema: Extended Follow-up Phase



- ▲ MRI, X-ray, WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score, pain in other joints, MOS SF-36, ICOAP, 20-meter walk test
 - △ WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score, pain in other joints, MOS SF-36, ICOAP, 20-meter walk test.
- Safety will be assessed at all visits.

Abbreviations: W: Week; EF: Extended Follow-up; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: Patient’s Global Assessment; KOOS QOL: Knee Injury and Osteoarthritis Outcome Score quality of life subscale; KOOS Symptom Index: Knee Injury and Osteoarthritis Outcome Score symptom index subscale; PGIC: Patient’s Global Impression of Change; NRS pain score: numerical rating scale pain score; MOS SF-36: Medical Outcomes Study Short Form-36 General Health Survey; ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain; MRI: magnetic resonance imaging.

Pain medications must be withheld for at least 5 half-lives before a visit involving completion of the WOMAC.

Adverse events, concomitant medications, and concomitant procedures (including concomitant surgical procedures on the target knee) will be monitored throughout the trial. Safety assessments during the extended follow-up phase are shown in [Appendix E](#).

Screening Period

The screening period will comprise a period of 4 to 42 days during which a subject’s eligibility for the trial will be determined, beginning at signature of the informed consent form (ICF) (Visit 1a). Subjects who have taken analgesia within 5 half-lives of the visit will be scheduled to return for complete screening procedures (Visit 1b) after a washout of all analgesic medications. Subjects not taking analgesic medication at the time of ICF signature may complete Visit 1a and 1b procedures at one visit. Screening will include completion of Question 1 of the WOMAC pain index and pain on an 11-point pain numerical rating scale (NRS) in both the target and contralateral knee. Subjects who have a WOMAC Question 1 score in the target knee of 4 to 9 after a predefined analgesic washout period equivalent to at least 5 half-lives of the analgesic medication(s) will continue with other screening procedures. During the screening period,

demographic and medical history data will be collected and subjects will undergo physical examination including height and weight and safety laboratory assessment (hematology, biochemistry, and urinalysis). X-rays will be taken of both knees, and the target knee will be identified.

If subjects fulfill all inclusion and no exclusion criteria (see Sections 5.3.1, 5.3.2, and 5.4), they will be randomized into the trial.

DBPC Treatment Phase

In the DBPC treatment phase, all subjects will receive 4 cycles of treatment with the IMP (sprifermin or matching placebo) at intervals of 6 months. Each cycle will consist of 3 once-weekly i.a. injections over a period of 3 consecutive weeks.

The DBPC treatment phase will begin at the baseline visit (Week 0/Visit 2), when eligibility will be confirmed, subjects will be randomized, and the first IMP injection will be administered.

Subjects will be randomized in equal allocation to one of the following treatment groups, as shown in [Figure 1](#) (randomization is described in Section 6.3).

- 4 cycles of sprifermin (100 mcg per injection)
- 2 cycles of sprifermin (100 mcg per injection) alternating with 2 cycles of placebo
- 4 cycles of sprifermin (30 mcg per injection)
- 2 cycles of sprifermin (30 mcg per injection) alternating with 2 cycles of placebo
- 4 cycles of placebo

The last of the four cycles of 3 injections of IMP will be given on Week 78/Visit 17, and the last dose of IMP is scheduled to be administered at Week 80/Visit 19. IMP administration for each treatment group is summarized in [Table 1](#), Section 6.2.

Major efficacy assessments will take place at intervals of 6 months, on the first day of each treatment cycle and at the end of the DBPC treatment phase (Week 104/Visit 22).

Minor efficacy assessments will also take place at intervals of 6 months, occurring 9 weeks after the end of each treatment cycle.

Details of DBPC treatment phase visits are presented in Section 7.1.3.

Efficacy assessments will include MRI and X-ray of the target knee, the WOMAC, the 20-meter walk test, and the Patient's Global Assessment of disease impact (PGA). The Knee Injury and Osteoarthritis Outcome Score QOL subscale (KOOS QOL) and the Medical Outcomes Study Short Form-36 General Health Survey (MOS SF-36) will be assessed for exploratory analysis of treatment effect on health-related QOL. The NRS will be used to explore treatment effect on worst pain in the past 24 hours in the target knee. The Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) and the KOOS Symptom Index questionnaires will be used to explore treatment effect on OA-related symptomatology in the target knee. The NRS pain scale

for the contralateral knee and a scale model of the human body (homunculus) identifying potentially painful joints will be used to assess pain in non-target joints and the progression of OA. The Patient Global Impression of Change (PGIC) will be used to measure the subject's assessment of the clinical importance of their improvement or worsening over the course of the trial.

At specified visits, blood samples will be collected for measurement of serum sprifermin/FGF-18 levels and biomarkers, and urine will be collected for measurement of biomarkers (see Section 7.6). These biomarker specimens will be collected after an 8-hour fast. At visits where IMP is injected, samples of synovial fluid will be collected for PK and biomarker assessment as part of the i.a. injection procedure, using the same needle that will be used for IMP injection.

Exploratory PGt analyses will be performed for subjects who provide separate informed consent.

AEs and concomitant medications and procedures will be monitored throughout the trial, and vital signs will be measured at each trial visit. Safety assessments will also include 12-lead electrocardiograms (ECGs), physical examination, weight measurements, safety laboratory analyses (hematology, biochemistry, and urinalysis), and testing for antibodies to sprifermin/FGF-18. Height will be measured at screening and at the end of the DBPC and extended follow-up phases. Data regarding any surgical procedures on the target knee will also be collected.

Subjects will use trial diaries to record information about AEs, concomitant medications, and local tolerability between trial visits. Diary information about maximum levels of target knee pain and presence or absence of target knee swelling will be used to identify potential acute inflammatory reactions (AIRs) to the IMP (see below).

Extended Follow-Up Phase

Subjects who complete the DBPC treatment phase visits will be followed for a further 3 years, during which trial assessments will take place at 6-month intervals.

Safety assessments will be performed and the WOMAC, NRS pain in the target and contralateral knee, KOOS QOL, KOOS Symptom Index, MOS SF-36, PGA, PGIC, identification of pain in other joints, ICOAP, and 20-meter walk test will be assessed at each visit during the follow-up phase. MRI and X-ray will be performed at yearly intervals.

Trial Endpoints

The primary endpoint of this trial is change from baseline in cartilage thickness in the total femorotibial joint as evaluated by MRI at 2 years.

Secondary endpoints are:

- Changes from baseline in the WOMAC total score and in the WOMAC pain, function, and stiffness index scores over 2 years
- Change from baseline in the 20-meter walk test over 2 years

- Change from baseline in the PGA over 2 years
- Change from baseline in minimal joint space width (JSW) in the medial and lateral compartments as evaluated by X-ray over 2 years
- Change from baseline in cartilage thickness in the medial and lateral compartments as well as in the total femorotibial joint over 2 years
- Change from baseline in cartilage volume in the medial and lateral compartments as well as in the total femorotibial joint over 2 years
- Synovial fluid levels of sprifermin/FGF-18
- Serum levels of sprifermin/FGF-18

Safety endpoints are:

- Nature, incidence and severity of local and systemic AEs
- Incidence of acute inflammatory reactions (AIRs), defined as increase of pain by 30 mm on a 100 mm VAS and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection (see Section 7.4.1.1)
- Changes in laboratory safety parameters, vital signs, 12-lead ECG parameters, weight, and physical examinations
- Incidence of surgical interventions in the target knee (including any surgical revision, cartilage removal, or any other type of surgical intervention)
- Occurrence of binding and neutralizing antibodies to sprifermin/FGF-18

Exploratory endpoints are:

- Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate (1) at 2 years
- PGIC over 2 years
- Changes from baseline in the scores of the KOOS QOL and the MOS SF-36 questionnaire over 2 years
- Change from baseline in KOOS Symptom Index over 2 years
- Change from baseline in NRS pain score in the target and contralateral knee over 2 years using an 11-point NRS
- Change from baseline in presence of pain in other joints over 2 years
- Change from baseline in ICOAP scores over 2 years
- Change over time in structural as well as compositional parameters of the knee joint (e.g., e.g., synovium, menisci, bone, and other structures) as evaluated by MRI
- Change from baseline in serum, urine, and synovial markers associated with administration of the compound

- Baseline protein markers and/or genetic markers associated with response to treatment or disease progression (response assessed by MRI and/or questionnaire)
- Changes in MRI outcomes, WOMAC scores, 20-meter walk test, PGA, PGIC, JSW, OMERACT-OARSI responder rate, KOOS QOL, KOOS Symptom Index, MOS SF-36, NRS pain score in the target and contralateral knee, presence of pain in other joints, ICOAP, safety laboratory values, and vital signs over the extended follow-up period and nature, incidence and severity of local and systemic AEs during the extended follow-up period (to be summarized descriptively)
- Relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time

Details of trial endpoints and their analysis are presented in Section 8.

Interim Analysis and Data Monitoring

No interim analysis is planned.

An IDMC will be constituted and will perform periodic reviews to evaluate the safety of the subjects participating in the trial on an ongoing basis. Detailed description of the safety monitoring will be specified in a dedicated IDMC charter.

Planned Duration of the Trial

It is estimated that the subject recruitment period for this trial will be up to one year.

It is anticipated that the first subject's first visit will take place in Aug 2013 and that the last subject's last visit (extended follow-up phase) will take place in August 2019.

It is planned to perform the statistical analysis in two steps, as described in Section 8.5.1: results from the DBPC treatment phase will be analyzed and reported at the end of this phase, and long-term follow-up data will be analyzed and reported separately. MRI readers, Investigators, and subjects will remain blinded during the extended follow-up phase.

5.2 Discussion of Trial Design

Overall Trial Design

The trial will consist of a screening period, a 2-year DBPC treatment phase, and a 3-year extended follow-up phase.

A screening period of up to 42 days is considered appropriate for assessment of subject eligibility. The screening period will include an assessment of pain levels at screening and baseline prior to randomization. The subject must have a pain score in the target knee of 4 to 9 in response to Question 1 of the WOMAC after a predefined washout period that will be equivalent to at least 5 half-lives of analgesic medication(s) to be eligible for the study (see Section 5.4).

The duration of the DBPC treatment phase of the trial will be set at 2 years in order to permit assessment of potential symptomatic and structural benefit. Results of the POC trial suggested that a period longer than 1 year would be necessary to observe treatment benefit on symptoms relative to placebo resulting from the demonstrated anabolic effect on structure.

The extended follow-up phase is intended to permit evaluation of the durability of the effects of sprifermin.

Sprifermin may be the first drug used in OA to have a disease-modifying action. In the absence of an active comparator, placebo will be used as a control.

A considerable placebo effect on symptoms in OA trials (with an effect size of 0.5 and a duration of 1 year) has been described in the literature (16), and was observed in the POC trial. In this trial, use of pain medication will be controlled to permit greater consistency of pain and function evaluations and eliminate the confounding effects of concomitant analgesia: subjects will need to refrain from taking analgesics, anti-inflammatory medications, or corticosteroids for ≥ 5 half-lives before a visit involving completion of the WOMAC. This requirement and the withdrawal of analgesic medication for 5 half-lives prior to pain assessments is a common practice in clinical trials in OA (17).

Subject Population

This trial will include symptomatic subjects who have sufficient residual cartilage to respond to sprifermin, and will include better control for external factors such as malalignment than the POC trial. The aim is to select a knee OA population where an improvement in structure may ultimately translate into improvements in symptoms and quality of life.

In the POC trial (Study 28980), an anabolic effect of sprifermin was demonstrated in subjects with Kellgren-Lawrence grades (KLG) of 2 or 3, confirming the appropriateness of Kellgren-Lawrence grades as a selection criterion.

However, in the POC trial, no minimal JSW was specified. The average JSW in the POC trial was approximately 3.5 mm and the minimum JSW was 0.2 mm. The requirement of JSW of at least 2.5 mm in the medial compartment in this trial will lead to the inclusion of patients with sufficient remaining interbone distance (i.e., a higher average JSW) that will thus permit demonstration of either progression (worsening) or improvement during the trial.

Malalignment will be limited to 5 degrees in order to limit confounding factors regarding biomechanical loading.

Women of childbearing potential will be allowed to participate in the trial, provided they adhere to the use of a highly effective method of contraception.

Dose and Dose Regimen

The aim of this trial is to optimize the dose and the dosing interval for sprifermin and to find a balance between effects on symptoms and structure.

OA is a chronic disease, and therefore treatment will most likely need to be repeated at regular intervals.

The use of repeated cycles of 3 once-weekly injections over 3 consecutive weeks is based on preclinical data generated in the dog meniscectomy model (see the sprifermin IB), which suggested that anabolic effects on cartilage tissue were more pronounced when a given dose of sprifermin was administered as three i.a. injections than when it was administered as a single injection.

In this trial, 2 dosage strengths of sprifermin (30 and 100 mcg) and 2 regimens (4 treatment cycles given at 6-month intervals and 2 treatment cycles given at a 12-month interval) will be used in this trial. Each regimen of sprifermin will be compared with placebo.

The 10 mcg dosage of sprifermin used in the POC trial will not be used in this trial: despite observation of some biological effect, there was limited effect on MRI or clinical outcomes with this dose. Furthermore, results from the POC trial suggested that an interval of 3 months between cycles may have been too short.

Trial Assessments

Evaluation of Structure by MRI and Choice of MRI as Primary Endpoint

Conventional radiography can visualize dense structures such as cortical and trabecular bone; however, other components of the human knee such as cartilage, menisci, ligaments, synovium, synovial fluid, and pathological alterations of bony structures such as cysts and edema can only be visualized with MRI (18). In recent years, MRI has been shown to have high inter-observer agreement among trained radiologists and to have a high internal validity in the assessment of OA through its ability to define soft-tissue structures with high precision. Thus, a comparison of MRI scans with conventional X-rays revealed that joint space narrowing was more due to loss of meniscal structure than loss of hyaline cartilage structure (19).

Change from baseline in cartilage thickness in the total femorotibial joint at 2 years as evaluated by MRI has been chosen as primary endpoint for this trial because this parameter is thought to be most appropriate for demonstrating reversal of the degeneration of cartilage tissue.

Change in total cartilage volume may be less sensitive than change in thickness, as it may not reflect growth of cartilage in regions of the knee that have importance in mechanical loading.

Because sprifermin has been shown to exert a structure-modifying effect, it appears imperative to use MRI data (specifically change in thickness) to either confirm or disprove this effect on cartilage structure.

Evaluation of Symptoms

The WOMAC is a validated instrument used to assess symptom modification in clinical OA trials. This clinical score was developed in 1981 and is regarded as a valid instrument by both

clinical researchers and regulatory authorities (20). The WOMAC questionnaire is further described in Section 7.3.2.

Considering that sprifermin has been shown to exert an anabolic effect on cartilage matrix, i.e., that it has a structure-modifying effect, it is expected that if it also has a symptom-modifying effect, this will become more evident in terms of the functional aspect of the WOMAC compared to those addressing pain and stiffness.

The 20-meter walk test will be used to provide an objective evaluation of the subject's physical functioning, to complement the results of the (subject-assessed) WOMAC function index score. This test consists of measuring the time needed for the subject to walk 20 meters at a normal pace.

In addition to the WOMAC, multiple questionnaires will be used to explore the treatment effect on the symptoms associated with OA. The Symptom Index subscale of the KOOS, a knee-specific questionnaire described in Section 7.7.1, will be used to assess symptoms associated with tibiofemoral cartilage loss. Pain, a major component of OA, will additionally be assessed using an 11-point NRS, evaluating the worst knee pain in the past 24 hours (Section 7.7.5). In addition, the ICOAP questionnaire will be used to explore the effect of treatment on intermittent and continuous OA pain (Section 7.7.3). Both of these assessments will complement the WOMAC pain index score.

Pain in other joints may be a confounding variable in the assessment of self-reported activities of daily living (WOMAC ADL), performance on the 20-meter walk test, and overall health-related quality of life (MOS SF-36). Pain in other joints may also serve as indicator of overall OA progression. Pain in the non-target knee will be assessed using the same 11-point NRS used in the target knee. In addition, pain in joints other than the knees will be identified using a scale model of the human body (homunculus; Section 7.7.6).

The PGA and PGIC will be used to capture the subject's global impression of their target knee pain and measure global improvement with treatment relative to baseline symptoms. As described in Sections 7.7.3 and 7.7.4, these are responsive and readily interpretable measures of participant's assessments of the clinical importance of their improvement or worsening over the course of the clinical trial.

Evaluation of JSW by X-ray

Change in joint space narrowing will be visualized with the "fixed flexion" knee radiograph protocol ((21); see Section 7.3.4).

Among rheumatologists, determination of joint space narrowing by X-ray is considered to be a semi-quantitative method for assessment of progression of knee OA. This outcome is recognized as valid by regulatory authorities in Europe and the USA (20),(22).

Evaluation of Safety

AE monitoring, safety laboratory measurements, measurement of vital signs, weight, physical examinations, ECGs, incidence of surgery, and, in case of a non-systemic drug, assessment of local tolerability are standard measures to evaluate the safety profile of an investigational product. Safety endpoints to be assessed in this trial are consistent with those used in previous studies with sprifermin.

One of the trial's safety endpoints is the incidence of acute inflammatory reactions (AIRs), defined as increase of pain by 30 mm on a 100 mm VAS and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection. A similar definition based on a 30-mm increase in pain on VAS and observation of local swelling was used successfully in a trial in rheumatoid arthritis involving i.a. injections of interleukin-1 receptor antagonist (IL-1ra; anakinra (23)).

The extension phase of the trial will allow exploration of the drug's long-term safety.

Biomarker Assessment

Assessment of biomarkers of bone and joint tissue turnover is expected to identify candidate markers potentially predictive of response to treatment, prognostic for disease progression, or associated with response to the compound (see Section 7.6.1.).

Pharmacokinetic Assessment

The levels of sprifermin/FGF-18 in serum will be assessed 2 hours after the last dose of each cycle and will give an indication of whether sprifermin reaches the systemic circulation. Based on previous trials, systemic levels of sprifermin/FGF-18 are expected to be below the LLOQ.

Levels of sprifermin/FGF-18 in synovial fluid will be measured in order to give a first estimate of the residence time of sprifermin in the synovial fluid.

Evaluation of Health-related Quality of Life

The KOOS (see Section 7.7.1) is a knee-specific questionnaire designed to evaluate both short-term and long-term consequences of knee injury, including OA; it is intended for use in knee injury potentially leading to post-traumatic OA or in primary OA. The KOOS QOL subscale is more specific to QOL in subjects with knee OA than the more general MOS SF-36 (see below), and may better predict future need for knee replacement.

The MOS SF-36 (see Section 7.7.2) is a generic patient-reported health-related QOL instrument that is widely used in different diseases and conditions (including OA). MOS SF-36 results from this trial will be used to determine whether the MOS SF-36 is sensitive enough to measure changes in QOL in the trial population.

5.2.1 Inclusion of Special Populations

The trial population will consist of adults aged between 40 and 85 years. The inclusion of elderly subjects is considered justified because this is the group most frequently affected by OA.

5.3 Selection of Trial Population

The trial will randomize approximately 545 subjects, in about 10 to 15 centers located in Europe, the United States of America, and possibly other geographical regions.

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Written informed consent given prior to any trial-related activity: subjects must understand and sign the appropriate approved Informed Consent Form(s) – one for the trial (mandatory) and one for the pharmacogenetic evaluation (optional)
2. Investigator judgment that the subject is able to comply with trial procedures and assessments
3. Primary femorotibial OA according to American College of Rheumatology (ACR) clinical and radiographic criteria (see [Appendix A](#))
4. Radiological grade of 2 or 3 according to Kellgren-Lawrence and a minimum joint space width (JSW) of ≥ 2.5 mm in the medial compartment in the target knee, obtained during screening.

Note: X-rays conducted up to 6 months prior to screening are acceptable, provided they were performed according to the specifications in the MOP and the quality is acceptable to allow confirmation of the entry criteria when read centrally.

5. Age from 40 to 85 years; of either sex
6. A history of pain due to OA in the target knee for at least 6 months
7. Pain in the target knee and/or the need for regular symptomatic treatment of knee pain with paracetamol (acetaminophen), systemic non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 selective inhibitors (coxibs), or tramadol on most days in the previous month (i.e., more than half of the days in the previous month)
8. Pain score for the target knee of 4 to 9 points in response to Question 1 of the WOMAC pain index (“how much pain have you had [in the target knee, over the past 48 hours] when walking on a flat surface?”) after washout of at least 5-half-lives of analgesic medication(s): acetaminophen, topical or oral NSAIDs, coxibs, opioids, and/or tramadol. The pain score must qualify at screening (Visit 1a for subjects not receiving analgesic medication at the time of screening and Visit 1b for subjects requiring a washout of analgesic medications) and baseline (Visit 2).
9. Women of childbearing potential (defined as any female subjects after puberty, unless postmenopausal for at least two years or surgically sterile) must use methods of contraception with a failure rate less than 1% per year when used consistently and correctly,

such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, vasectomized partners, or a double barrier method (use of both a condom and a diaphragm or cervical/vault cap) with spermicide. Contraceptive use must be continued throughout the throughout the trial (i.e., until the final extended follow-up visit).

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Malalignment of > 5 degrees in the femorotibial axis of the target knee as assessed by the X-ray with a long-axis view that will be performed during screening
2. Intra-articular administration of corticosteroids or hyaluronic acid into either knee within 6 months, or arthroscopy to the target knee within the past year before the start of screening
3. Planned knee surgery (affecting either the target or the contralateral knee) within the next two years
4. Clinical signs of inflammation (i.e., redness) in the target knee
5. Concomitant treatment with any parenteral or oral corticosteroids at study entry
6. Concomitant treatment with parenteral, oral, or topical opioids at study entry, with the exception of oral tramadol
7. Concomitant treatment with a parenteral or oral anticoagulant including heparin, coumadin/warfarin or their derivatives, or any other anticoagulant.
8. History of sarcoma or other malignancy within the past five years, except adequately treated basal cell or squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ.
9. Secondary OA such as joint dysplasia, aseptic osteonecrosis, acromegaly, Paget disease, Ehlers-Danlos syndrome, Stickler syndrome, joint infection (septic arthritis), hemochromatosis, gout, chondrocalcinosis (pseudogout), or calcium pyrophosphate deposition disease.
(Exception: subjects who have undergone meniscal resection may be enrolled.)
10. Plan to relocate from the region
11. Previous participation as a subject in another trial of sprifermin
12. Any contraindication to MRI according to MRI guidelines, including the inability to undergo a knee MRI exam because of inability to fit in the scanner or knee coil
13. Significant co-morbidity that would interfere with trial participation
14. Any known active infection, including suspicion of intra-articular infection or infection that might compromise the immune system such as human immunodeficiency virus (HIV) or hepatitis B or C
15. Abnormal laboratory results including:
 - Hemoglobin < 11.5 g/dL (female) or < 13.2 g/dL (male)

- White blood cell (WBC) count < 3500 cells/mm³ and >20000 cells/mm³
 - Platelet count or coagulation tests (prothrombin time, partial thromboplastin time, International Normalized Ratio) outside the central laboratory's normal range
 - Creatinine clearance rate < 30 mL/min estimated using the Cockcroft-Gault formula
 - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2.5 times ULN, or total bilirubin > 1.5 x ULN. In cases of documented Gilbert syndrome, subjects with elevated bilirubin levels will be permitted to enroll in the study if other liver function tests are within the specified limits.
 - Any other abnormal laboratory results that the Investigator believes should preclude the subject's participation in the trial
16. Pregnancy or breastfeeding
17. Participation in another clinical trial within the 30 days (or 5 half-lives of the investigated compound, whichever is longer) before screening
18. Known hypersensitivity to the trial treatment (including placebo) or diluent
19. Legal incapacity or limited legal capacity

5.4 Criteria for Randomization

Subject's pain level will be assessed during the screening, and eligibility will be confirmed at baseline.

- As an essential part of the eligibility determination process, subjects will be asked to complete Question 1 of the WOMAC pain index ("How much pain have you had [in the target knee, over the past 48 hours] when walking on a flat surface?"; see [Appendix C](#)).

The WOMAC questions that determine eligibility must be obtained after the patient has provided informed consent and, if taking pain medications, has withheld them, as described below.

- Subjects who are taking pain medications and who are potentially eligible for the trial will be asked to withhold all pain medications including paracetamol (acetaminophen), NSAIDs including coxibs, opioids, and tramadol for at least 5 half-lives of the given medication before the screening (Visit 1b) and baseline (Visit 2) WOMAC assessments.

Aspirin (acetylsalicylic acid) used for cardiovascular protection does not need to be withheld, nor do antidepressants used for management of OA pain and depression.

Subjects must have a score of 4 to 9 points for Question 1 of the WOMAC pain index at the time of screening (after washout of analgesic medications).

- To be eligible for randomization subjects must again respond with a score of 4 to 9 in response to Question 1 on the WOMAC at the time of the baseline visit - after washout of pain medications for a period of at least 5 half-lives.

Subjects who satisfy all eligibility criteria and who are willing to continue in the trial will be randomized as described in Section 6.3. Randomization and administration of the first IMP injection will take place on the same day as the baseline MRI scan (see Section 7.1.3.1).

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons.

The Investigator may withdraw a subject at any time if this is considered to be in the subject's best interest.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent
- Subject's participation in another trial

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, the procedures scheduled for Week 104/Visit 22 should be performed at the time of withdrawal whenever possible, with focus on the most relevant assessments. In any case, the appropriate Case Report Form section must be completed.

Subjects who withdraw from the trial will not be replaced.

5.5.2 Withdrawal from the Investigational Medicinal Product

Treatment with the IMP must be discontinued in the event of any of the following:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor
- Occurrence of AEs, if discontinuation of trial drug is desired or considered necessary by the Investigator and/or the subject
- Occurrence of pregnancy (see Section 7.4.2 for reporting of pregnancies and follow-up of subjects who become pregnant during the trial)
- Use of a non-permitted concomitant medication, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP
- Substantial non-compliance or protocol violation

Subjects who discontinue IMP treatment prematurely will be followed up as described in Section 7.1.5.

5.6 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- Recommendation by the trial’s IDMC.
- New information leading to unfavorable risk-benefit judgment of the IMP, e.g., due to:
 - Evidence of lack of efficacy of the IMP,
 - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
 - Other unfavorable safety findings.
- Sponsor’s decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of the Sponsor’s IMP.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended at the request of Health Authorities.

5.7 Definition of End of Trial

For administrative and safety reporting purposes, the end of the trial will be defined as the date of the final clinical database lock at the end of the extended follow-up phase. This provides for a single and conservative definition across all trial sites.

6 Investigational Medicinal Products and Other Drugs Used in the Trial

The term “Investigational Medicinal Product” (IMP) refers to both the investigational drug undergoing trial (sprifermin) and the placebo.

6.1 Description of Investigational Medicinal Products

Clinical trial materials are manufactured in accordance with Good Manufacturing Practice (GMP). All clinical trial materials will be supplied with Certificates of Analysis and/or Release Statements. Trial drugs will be identified by trial code, kit number, and Sponsor name.

IMP packaging and labeling are described in Section 6.6; IMP preparation, handling, and storage are described in Section 6.7 and in the MOP.

6.1.1 Sprifermin

Sprifermin is a truncated, non-glycosylated form of FGF-18, containing 170 amino acids.

Two strengths of sprifermin will be supplied in this trial: 30 mcg and 100 mcg.

Sprifermin will be supplied as a white, sterile, freeze-dried powder in 3-mL glass vials, sealed with rubber stoppers, flip-off caps and aluminum rings. Each vial will contain either 31.5 mcg or 105 mcg of sprifermin active substance; these quantities will include a 5% overage, permitting extraction of respectively 30 mcg or 100 mcg of sprifermin active substance following reconstitution with 0.9% w/v Sodium Chloride Injection (referred to herein as “saline solution”). Excipients of the formulation are sodium phosphate buffer (pH 7.2), sodium hydroxide, O-phosphoric acid, sucrose, and poloxamer 188.

For all treatment groups, the volume to be administered is 2 mL.

6.1.2 Placebo

Placebo will be supplied as a white, sterile, freeze-dried powder visually identical to the active product, and will be supplied in packaging identical to that for sprifermin. The excipients will be identical to those in the active product.

6.2 Dosage and Administration

In the DBPC treatment phase, all subjects will receive 4 cycles of treatment with the IMP (sprifermin or matching placebo) at intervals of 6 months. Each cycle will consist of 3 once-weekly i.a. injections over a period of 3 consecutive weeks.

IMP administration for each treatment group is summarized in Table 1.

Table 1 Drug Administration Diagram

	Cycle 1 W0, W1, W2	Cycle 2 W26, W27, W28	Cycle 3 W52, W53, W54	Cycle 4 W78, W79, W80	Dose per cycle	Total dose
Group 1	100 mcg	100 mcg	100 mcg	100 mcg	300 mcg	1200 mcg
Group 2	100 mcg	Placebo	100 mcg	Placebo	300 mcg/placebo	600 mcg
Group 3	30 mcg	30 mcg	30 mcg	30 mcg	90 mcg	360 mcg
Group 4	30 mcg	Placebo	30 mcg	Placebo	90 mcg/placebo	180 mcg
Group 5	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Each cycle consists of 3 once-weekly i.a. injections of the specified dose over 3 consecutive weeks.

The central randomization service’s interactive voice response system (IVRS) will be used to randomize subjects and to assign a blinded treatment kit at each treatment visit, as described in Section 6.3.

Each treatment kit will include materials for a single injection.

All kits will include 1 glass vial of IMP (sprifermin or placebo) and 1 glass ampule of sterile saline solution for injection (2 mL per ampule) to be used for reconstitution (see Section 6.6).

Instructions for reconstitution are provided in the MOP. Once reconstituted, the IMP may remain in the syringe for up to 2 hours prior to administration.

The Investigator or a suitably qualified designee will administer the IMP. The exact time of IMP administration will be documented in the CRF.

I.a. administration of the IMP will be guided through the use of ultrasound to ensure delivery into the joint space. Detailed instructions for injection are provided in the MOP.

Before injecting the IMP solution, an aspiration of the synovial fluid for local PK and biomarker analysis will be performed as part of the i.a. injection procedure, using the same needle that will be used for IMP injection. If possible, up to 2.5 mL should be collected (instructions for sample handling are provided in the MOP).

The volume of IMP solution to be injected will be 2 mL. The needle for injection will be flushed with 0.5 mL saline to make sure the entire dose has been injected (thus, the total volume injected will be 2.5 mL).

At visits where samples are collected for PK analyses, subjects will be requested to stay in the study site for approximately 2 hours post-injection for collection of the post-dose samples.

6.3 Assignment to Treatment Groups

Eligible subjects will be randomized to one of the 5 treatment groups with an allocation ratio of 1:1:1:1:1. Statistical aspects of randomization are described in Section 8.2.

The central randomization service's IVRS will be used to randomize subjects to treatment. Immediately prior to dosing, the Investigator or delegate will follow randomization procedures as explained in the MOP. The allocated randomization number will only be used for dosing.

The IVRS will also be used to assign a blinded treatment kit at each subsequent treatment visit (see Section 7.1.3.2 and Appendix E).

6.4 Other Drugs to be used in the Trial

No other drugs will be provided in the context of this trial.

6.5 Concomitant Medications and Therapies

6.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the CRF.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant medication must be recorded in the corresponding section of the CRF, noting the name, dose, frequency of administration, duration, and indication of each medication.

During the screening period, all analgesic medication must be withheld for 5 half-lives before the screening (Visit 1b) and baseline WOMAC assessments. Aspirin (acetylsalicylic acid) used for cardiovascular protection does not need to be withheld, nor do antidepressants used for management of OA pain or depression.

Paracetamol (acetaminophen), NSAIDs including coxibs, and tramadol may be resumed following randomization and continued as needed during the trial, except during the brief analgesic withdrawal periods prior each study visit at which WOMAC data are obtained.

During the trial, paracetamol (acetaminophen) is recommended as rescue medication for the treatment of breakthrough pain. The dosage of acetaminophen or paracetamol that the subjects will be allowed to take per day will be defined according to the standard of care in the countries where the trial will be carried out; however, the maximum dose should not exceed 1 gram per dose and 4 grams/day. Low-dose narcotics or combination products such as paracetamol/acetaminophen and oxycodone (Percocet) may be used only as needed for more severe painful episodes. Duration of opioid use is limited to 14 days per episode. If the subject requires regular narcotic analgesia to control his/her arthritis pain, s/he should not be considered for the trial.

After the initial screening visit (Visit 1a), subjects will be requested to discontinue the intake of all pain medications, including NSAIDs, coxibs, narcotics, and paracetamol (acetaminophen) for at least 5 half-lives before a visit involving completion of the WOMAC, as described in Section 7.1.1. This is to ensure the most accurate assessment of pain and function, and is standard practice in OA trials. Aspirin (acetylsalicylic acid) used for cardiovascular protection does not need to be withheld, nor do antidepressants used for management of OA pain or depression.

Oral supplements such as glucosamine, diacerin, chondroitin sulfate may be used during the trial if they have been taken at a stable dose over at least 4 weeks prior to the first injection and are maintained at the same stable dose throughout the trial.

Women of childbearing potential must use a method of contraception with a failure rate less than 1% per year (as defined in the trial inclusion criteria; see Section 5.3.1) throughout the trial (i.e.,

until the final extended follow-up visit). In case of premature withdrawal from the trial, there is no specific requirement for contraceptive use after the last trial visit.

Local anesthetic (e.g., lidocaine) is permitted prior to the injection of IMP at the investigator's discretion according to the local standard of care. Anesthetic should not be administered intra-articularly at any time.

6.5.2 Non-permitted Medicines

Subjects who have received i.a. corticosteroids or i.a. hyaluronic acid within the 6 months before the beginning of screening will not be eligible for this trial, nor will subjects who are receiving concomitant treatment with oral corticosteroids or with a parenteral or oral anticoagulant, including heparin, coumadin/warfarin or their derivatives, or any other anticoagulant.

Subjects who have taken part in another clinical trial within the 30 days (or 5 half-lives of the investigated compound, whichever is longer) before the beginning of screening or in any previous trial of sprifermin will not be eligible.

Use of the following medications is not permitted at any time during the trial (i.e., from signature of the Informed Consent Form (ICF) until the final trial visit (end of extended follow-up phase or early termination):

- Intra-articular injection of corticosteroids or hyaluronic acid into either knee
- Long-term treatment (>14 days) with oral corticosteroids >5 mg/day

Note: However, the use of oral corticosteroids, ≤ 5 mg/day oral prednisone (or equivalent) for an indication other than OA pain during the trial will be allowed. In addition, short term use of any tapering course of oral corticosteroids for ≤ 14 days will be allowed. If oral corticosteroids >5 mg/day are used during the trial, efficacy assessments (e.g., WOMAC) should not be scheduled until it has been at least 5-half lives since completing the medication

- Any parenteral or oral anticoagulant, including heparin, coumadin/warfarin, or their derivatives, or any other anticoagulant medications
- Any investigational agent

If the administration of a non-permitted concomitant medication becomes necessary during the trial, e.g., because of AEs, treatment with the IMP will be discontinued and the subject will be followed up as described in Section 7.1.5.

Subjects who receive any investigational treatment or participate in any other trial will be withdrawn from this trial.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant medications must be recorded in the corresponding section of the CRF, noting the name, dose, frequency of administration, duration, and indication of each medication.

6.5.3 Other Trial Considerations

Other Permitted Therapies

Patient education and physical or occupational therapy (e.g., assisting device for walking, diet for weight loss, muscle-strengthening exercises) are allowed.

Other Non-Permitted Therapies

Interventional or diagnostic arthroscopy affecting the target knee is not permitted.

Use of electrotherapy (e.g., transcutaneous electrical stimulation) or acupuncture for OA affecting the target knee is not permitted.

If any of these procedures are used during the trial, treatment with the IMP will be discontinued and the subject will be followed up as described in Section 7.1.5.

6.5.4 Special Precautions

No special precautions are necessary beyond those applicable to i.a. administration in general.

6.6 Packaging and Labeling

IMP (sprifermin and placebo) will be provided in glass vials as described in Section 6.1.1.

Packaging and labeling will be identical for placebo and active medication to ensure the blinded nature of the trial, and will be in accordance with applicable local regulatory requirements and applicable GMP guidelines and with the storage requirements of the IMP.

Vials of IMP will come in kits as described in Section 6.2. All kits will contain 1 vial of IMP (sprifermin or placebo) and 1 ampule of sterile saline solution for reconstitution:

- Kits for 30 mcg treatments will contain 1 glass vial of sprifermin (30 mcg strength) and 1 glass ampule of sterile saline solution for injection (2 mL per ampule)
- Kits for 100 mcg treatments will contain 1 glass vial of sprifermin (100 mcg strength) and 1 glass ampule of sterile saline solution for injection (2 mL per ampule)
- Kits for placebo treatments will contain 1 glass vial of placebo and 1 glass ampule of sterile saline solution for injection (2 mL per ampule)

6.7 Preparation, Handling and Storage

Preparation and administration of the IMP are described in Section 6.2 and in the MOP.

Once reconstituted, the IMP may remain in the syringe for up to 2 hours prior to administration.

The IMP must be stored at ambient temperature (< 25°C; do not freeze) in a locked dispensary, with a temperature log maintained daily. It will be transferred to the clinical unit when needed for administration to the subjects.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring accountability for IMP, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the distribution center and returning it to the distribution center. A copy will be retained for the Investigator File.
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the Monitor and an accurate accounting will be available for verification by the Monitor at each monitoring visit.
- IMP accountability records will include:
 - Confirmation of IMP delivery to the trial site.
 - The inventory at the site of IMP provided by the distribution center and prepared at the site.
 - Administration of each dose to each subject.
 - The return to the distribution center or alternative disposition of unused IMP.
 - Dates, quantities, batch numbers, expiry dates and (for IMP prepared at the site) formulation, as well as the subjects' trial numbers.
- The Investigator should maintain records that adequately document:
 - That the subjects were administered the doses specified by the clinical trial protocol/amendment(s), and
 - That all IMP provided by the distribution center was fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. IMP that has been dispensed to a subject must not be re-dispensed to a different subject.

The Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the distribution center or authorizing their destruction by the trial site.

6.9 Assessment of Investigational Medicinal Product Compliance

The Investigator or a suitably qualified designee will administer the IMP. IMP administration must be recorded in the CRF.

6.10 Method of Blinding

The Sponsor will supply active sprifermin and placebo in glass vials which will be visually identical. Packaging and labeling will be identical for placebo and active medication (see Section 6.6).

At each trial visit at which IMP is administered, the central randomization service's IVRS will be used to obtain a blinded treatment kit number corresponding to the subject's randomized treatment (see Section 6.3). The subject will then be treated with the medication from that numbered kit.

All kits will include 1 glass vial of IMP (sprifermin or placebo) and 1 glass ampule of sterile saline solution for injection (2 mL per ampule) to be used for reconstitution (see Section 6.6). Reconstitution of IMP and preparation of injections will be identical for all treatments (sprifermin 100 mcg, sprifermin 30 mcg, and placebo).

6.11 Emergency Unblinding

The trial blind may be broken for an individual subject only in the case of an emergency when knowledge of the IMP is essential for the clinical management of the subject. The Investigator must make every effort to contact the Sponsor prior to breaking the trial blind.

If it is not possible to contact the Sponsor, the Investigator will be able to access the subject's treatment assignment 24 hours a day through the IVRS system, using specific procedures defined in the MOP.

Contact information for breaking the blind in an emergency will also be provided on the subject emergency card handed out to each subject (see Section 9.4).

If the blind is broken, the Investigator must inform the Sponsor immediately without revealing to the Sponsor personnel the result of the code break. The Investigator must record in the subject's CRF the date of unblinding and the reason for unblinding. Code breaks performed at a place other than the trial site will also be documented carefully.

If emergency unblinding is required, discontinuation of the affected subject from the trial is not mandatory unless there are other circumstances that require subject discontinuation.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in the clinical trial protocol (i.e., 100 mcg). Any overdose must be recorded in the trial medication section of the CRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the Sponsor's Global Drug Safety (GDS) department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

The effects of an overdose of sprifermin are unknown, and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be closely monitored and managed according to the Investigator's clinical judgment.

6.13 Medical Care of Subjects after End of Trial

Subjects who have completed the trial or have withdrawn early should be managed in accordance with the Investigator's clinical judgment, as appropriate for each subject's individual medical needs.

7 Trial Procedures and Assessments

Outlines of trial procedures and assessments are presented in Section 7.1. Procedures and assessments are described in more detail in Sections 7.2 (baseline characteristics), 7.3 (efficacy), 7.4 (safety), 7.5 (PK), 7.6 (biomarkers), and 7.7 (assessment of health-related QOL and OA pain).

7.1 Schedule of Assessments

The trial will consist of a screening period, a DBPC treatment phase (which will begin with randomization and initiation of therapy at Week 0/Visit 2), and an extended follow-up phase (see Section 5.1, [Figure 1](#), and [Figure 2](#)).

General instructions and procedures to be performed throughout the trial are described in Section 7.1.1, and outlines of the visits included in each of the trial phases are presented in Sections 7.1.2 (screening period), 7.1.3 (DBPC treatment phase), and 7.1.4 (extended follow-up phase).

The procedures to be performed at each trial visit are presented in the Schedule of Trial Procedures in [Appendix E](#).

7.1.1 General Instructions

Informed Consent

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2.

Subjects who agree to take part in the optional PGt analysis will also need to sign a specific PGt ICF.

Assignment of a Subject Identifier

Once a subject has provided written informed consent for trial participation, a subject identification number will be assigned through the IVRS. Subjects will be referred to by their subject identification number throughout the trial.

Subjects Who Fail Screening

The Investigator is required to maintain a subject screening log to identify the subjects who were screened.

In the CRFs, the minimum information to be recorded for subjects who fail screening is:

- Informed consent
- Demographics
- AEs
- Date and reason for screening failure
- Investigator signature

Adverse Events and Concomitant Medications

Information about AEs and about concomitant medications and procedures will be collected throughout the trial, beginning at the time of signature of the ICF (see Sections 7.4.1 and 6.5).

Allowable Time Frame for Trial Visits and Assessments

Study visits, beginning with Visit 3, should be planned for the study day specified in the protocol. Visits should always be scheduled from the date of the first injection (Week 0/Visit 2) while maintaining the minimum and maximum restrictions between injections and between injection cycles. If a visit cannot be completed within the study days specified in this section the sponsor should be contacted.

Allowable intervals between weekly IMP injections:

The interval between each injection within a treatment cycle should be 7 days. If it is not possible to complete the visit in exactly 7 days, or if an emergency occurs, the interval to the next injection should be no shorter than 6 days and no longer than 9 days (i.e., -1/+2 days). This interval allowance applies to Visits 3, 4, 8, 9, 13, 14, 18, and 19.

Allowable intervals between six month treatment cycles:

The interval between the last injection of a treatment cycle and the first injection of the subsequent treatment cycle is 24 weeks. If a visit cannot be done as planned, or if an emergency occurs, it can be rescheduled ± 3 weeks from the planned day (i.e., between 21 and 27 weeks). Specifically:

- Visit 7 must be conducted within 21 to 27 weeks of the actual date of Visit 4,
- Visit 12 must be conducted within 21 to 27 weeks of the actual date of Visit 9, and
- Visit 17 must be conducted within 21 to 27 weeks of the actual date of Visit 14

Allowable intervals for other visits:

During the DBPC treatment phase, visits may take place within ± 4 days of the planned day. This interval allowance applies to Visits 5, 6, 10, 11, 15, 16, 20, and 21.

Extended follow-up visits may take place within ± 21 days of the planned day. This interval allowance applies from Visit 22 (EF1) through Visit 28 (EF6).

Allowable intervals for X-rays and MRIs:

At time points where IMP administration is scheduled, X-rays and MRIs may be performed up to 3 days before the IMP administration.

During the DBPC phase, at time points where there is no IMP administration scheduled, X-rays and MRIs may be performed within ± 4 days of the planned day.

During the extended follow up phase, at time points when there is no IMP administration scheduled, X-rays and MRIs may be performed within ± 7 days of the planned day.

Pain Medication Washout

Subjects will be requested to discontinue the intake of all pain medications for 5 half-lives before a visit involving completion of the WOMAC. At least 3 days before each such visit, subjects will be contacted by phone to remind them of this requirement.

Aspirin (acetylsalicylic acid) used for cardiovascular protection does not need to be withheld, nor do antidepressants used for management of OA pain or depression.

Subject Questionnaires

At visits involving completion of subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score in the target and contralateral knee, MOS SF-36, pain in other joints, and ICOAP), these questionnaires must be completed before any other trial procedures are performed. The WOMAC should be completed first.

Subject Diaries

Subjects will receive diaries at each visit for recording of the following information:

- Any adverse reaction occurring between trial visits and any concomitant medications used, with particular attention to the use of NSAIDs, coxibs, and any other pain medications
- Maximum pain level (using a 100-mm VAS) and presence or absence of joint swelling, to be recorded once daily on the day before each IMP injection and on each of the 3 days following an IMP injection.
 - Diaries given at the visit before the beginning of a treatment cycle (e.g., screening or Week 12/Visit 6) will collect pain and swelling information for the day before the next visit. Telephone contacts concerning the need to withhold pain medications before the next visit will include a reminder to complete this diary information.

- Diaries given at visits where the first and second doses of a cycle are administered will collect pain and swelling information for the 3 days after the injection and for the day before the next visit.
- Diaries given at visits where the last dose of a cycle is administered will collect pain and swelling information for the 3 days after the injection.
- Diaries given at all other visits will collect adverse reactions and concomitant medications only.

Different diaries will be dispensed, depending on the data to be completed prior to the next visit. Completed diaries will be collected and reviewed at each visit, and information will be transcribed to the CRFs (following medical review in case of AE or concomitant medication information).

Pharmacogenetic Analysis

All subjects who are enrolled in the trial will be eligible to participate in an optional PGt analysis (except in countries where collection of PGt samples is not allowed; the analysis is described in Section 7.6.3). Participation is optional, and the subjects who choose to participate will need to sign a specific PGt ICF (see Section 9.2).

For consenting subjects, a single blood sample will be collected for PGt analysis. This sample can be obtained at any trial visit, preferably at baseline.

7.1.2 Screening Period (Visits 1a and 1b)

The screening period will comprise a period of 4 to 42 days before the baseline visit, beginning at signature of the ICF, during which a subject's eligibility for the trial will be determined.

Eligibility will be confirmed at the baseline visit (Week 0/Visit 2) as described in Section 5.4.

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent according to the procedure described in Section 9.2.

Visit 1a

The following procedures will be performed during the subject's first screening visit.

- Informed consent for trial
- Informed consent for optional PGt analysis
- WOMAC (Question 1 of the WOMAC pain index only; see Section 5.4 and Appendix C): this assessment should be done after informed consent is obtained and before any other procedures or examinations are performed. The question should be answered for both knees, since the target knee has not yet been identified.
- PGA (see Section 7.3.3)

- NRS pain score for both knees
- Collection of demographic characteristics (see Section 7.2)
- Medical/medication history (see Section 7.2)

Subjects will be asked to withhold all pain medications, including narcotics and paracetamol (acetaminophen) for 5 half-lives and a visit will be scheduled to continue screening. Aspirin (acetylsalicylic acid) used for cardiovascular protection does not need to be withheld, nor do antidepressants used for management of OA pain or depression.

Subjects not taking analgesic medication at the time of informed consent signature can have Visit 1a and 1b procedures completed at the same visit.

Visit 1b

The following procedures are to be performed in all subjects. Subjects taking analgesic medications at the time of Visit 1a must undergo washout of all analgesic medications and schedule a follow-up visit as described above. Subjects not taking analgesic medications can proceed with the following procedures at the time of the initial study visit.

- WOMAC (Question 1 of the WOMAC pain index only; see Section 5.4 and Appendix C): this assessment should be done before any other procedures or examinations are performed and completed for both knees, since the target knee has not yet been identified.
- NRS pain score for the target and contralateral knee
NOTE: if Visit 1a and 1b are being combined do not repeat the WOMAC Question 1 or the NRS pain score.
- Review of AEs and concomitant medications (see Sections 7.4.1 and 6.5)
- Vital signs measurement (see Section 7.4.4)
- Physical examination, including height and weight
- 12-lead ECG (see Section 7.4.4)
- Sample collection for hematology, biochemistry, and urinalysis (see Section 7.4.3 and Appendix B): coagulation tests will also be performed during the screening period (to be done locally).
- Serum pregnancy test for women of childbearing potential
NOTE: In women of childbearing potential, a negative serum pregnancy test must be obtained before knee X-rays.
- 20-meter walk test (see Section 7.3.5)
- X-rays of both the target knee and the contralateral knee, plus a long-axis view of the target knee (see Section 7.3.4)
- Identification of the target knee
- Review of inclusion and exclusion criteria (see Sections 5.3.1 and 5.3.2)

These procedures can be spread out over the screening period if this is necessary for logistical reasons. However, subject questionnaires (WOMAC Question 1, PGA, and NRS pain) must be done on the same day at the beginning of screening. Subjects must have a pain score for the target knee of 4 to 9 points in response to Question 1 of the WOMAC pain index after drug washout at the time of Visit 1b to be eligible for continued screening.

Subjects will again be asked to withhold all pain medications, including narcotics and paracetamol (acetaminophen) for 5 half-lives before the baseline WOMAC assessment (Visit 2).

At the beginning of the screening period, subjects will be given trial diaries for recording of any AEs occurring or concomitant medications used during screening and for recording of maximum pain and presence or absence of joint swelling in the target knee on the day before the first IMP administration (Week 0/Visit 2; see Section 7.1.1).

7.1.3 Double-Blind Placebo-Controlled Treatment Phase (Visits 2 to 22)

The duration of the DBPC treatment phase will be 2 years (104 weeks). Trial visits during this phase are outlined in [Table 2](#), and details of the procedures to be performed are presented in [Appendix E](#).

Table 2 Trial Visits during DBPC Treatment Phase

Visit Number	Week*	Treatment	Visit Name or Type
2	0	X	Baseline – Major Efficacy
3	1	X	
4	2	X	
5	3		
6	12		Minor Efficacy
7	26	X	Major Efficacy
8	27	X	
9	28	X	
10	29		
11	38		Minor Efficacy
12	52	X	Major Efficacy
13	53	X	
14	54	X	
15	55		
16	64		Minor Efficacy
17	78	X	Major Efficacy
18	79	X	
19	80	X	
20	81		
21	90		Minor Efficacy
22	104		Major Efficacy

* Relative to randomization and initiation of therapy at Week 0. Assessments performed at “major” and “minor” efficacy visits are described in Sections 7.1.3.3 and 7.1.3.4 respectively.

Subject eligibility for the trial will be confirmed at the baseline visit (Week 0/Visit 2; see Section 7.1.3.1) based on scores for Question 1 of the WOMAC pain index at screening and baseline (see Section 5.4). Eligible subjects will then be randomized and the first i.a. injection of IMP will be administered.

I.a. injections of the IMP will be administered at the baseline visit (Week 0/Visit 2) and at the visits identified in Section 7.1.3.2.

Major efficacy assessments will take place at intervals of 6 months, at the beginning of each treatment cycle and at the end of the DBPC treatment phase (Week 104/Visit 22; see Section 7.1.3.3).

Minor efficacy assessments will also take place at intervals of 6 months, occurring 9 weeks after the end of each treatment cycle (see Section 7.1.3.4).

Subjects will be requested to discontinue the intake of all pain medications for 5 half-lives before a visit involving completion of the WOMAC (see Sections 5.4 and 7.1.2). At least 3 days before each such visit, subjects will be contacted by phone to remind them of this requirement. When

the upcoming visit includes injection of IMP, this phone contact will include a reminder to complete trial diary information about target knee pain and swelling for the day before the visit.

Vital signs measurement (see Section 7.4.4) and review of AEs and concomitant medications (see Sections 7.4.1 and 6.5) will be performed at all DBPC treatment phase visits.

For women of childbearing potential, urine pregnancy tests will be performed before dosing on each treatment day (see Section 7.1.3.3).

Blood samples will be collected for testing for antibodies to sprifermin/FGF-18 at the baseline visit and at major efficacy visits (see Section 7.1.3.3), and also one week after the last dose of each treatment cycle (at Weeks 3, 29, 55, and 81/Visits 5, 10, 15, and 20).

Blood samples will be collected for PK analysis at the baseline visit (Week 0/Visit 2), at the end of each treatment cycle (Weeks 2, 28, 54, and 80/Visits 4, 9, 14, and 19), and at the end of the DBPC treatment phase (Week 104/Visit 22). PK samples will be taken pre-injection at baseline and 2 hours post-injection at subsequent visits where IMP is administered.

Fasting blood and urine samples for biomarker analysis will be collected at the baseline visit (Week 0/Visit 2) and at other visits (see Appendix E). For time points where IMP injections are administered, samples will be collected pre-dose. For urine, second morning void samples should be obtained.

12-lead ECGs will be performed at Week 52 (Visit 12; pre-dose) and Week 104 (Visit 22).

At each visit, subjects will be given trial diaries for recording of any AEs occurring or concomitant medications used between visits and for recording of maximum pain and presence or absence of joint swelling in the target knee for the day before and the 3 days after each IMP injection (see Section 7.1.1). Diaries will be collected and reviewed at the following visit.

7.1.3.1 Baseline Visit (Week 0; Visit 2)

The baseline visit must take place within 42 days after the beginning of screening, following the pain medication washout necessary for confirmation of trial eligibility (see Section 5.4).

The following procedures will be performed at the baseline visit before administration of IMP. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, NRS pain score in the target and contralateral knee, pain in other joints, MOS SF-36, and ICOAP) should be completed before any other procedures are performed; the WOMAC should be completed first.

- WOMAC (see [Appendix C](#))
- PGA (see [Section 7.3.3](#))
- KOOS QOL (see [Appendix D](#))
- KOOS Symptom Index (see [Appendix D](#))
- NRS pain (see [Section 7.7.5](#))
- Pain in other joints (see [Appendix F](#))
- MOS SF-36 (see [Appendix C](#))
- ICOAP (see [Appendix C](#))
- Review of AEs and concomitant medications (see [Sections 7.4.1](#) and [6.5](#))
- Review of subject diaries (see [Section 7.1.1](#))
- Vital signs measurement (see [Section 7.4.4](#))
- Sample collection for hematology, biochemistry, and urinalysis (see [Section 7.4.3](#) and [Appendix B](#))
- Blood collection for testing for antibodies to sprifermin/FGF-18 (see [Section 7.4.3](#))
- Blood collection for PK analysis (see [Section 7.5.1](#))
- Blood collection (fasting) for biomarker analysis (see [Section 7.6.2](#))
- Blood collection for optional PGt analyses (for subjects who have signed the PGt informed consent). If a blood sample cannot be obtained at the baseline visit, this sample can be taken at any subsequent visit (see [Section 7.6.3](#)).
- Urine collection (second morning void) for biomarker analysis (see [Section 7.6.2](#))
- Urine pregnancy test for women of childbearing potential
- 20-meter walk test (see [Section 7.3.5](#))
- Target knee MRI (see [Section 7.3.1](#))
- Review of inclusion and exclusion criteria (see [Sections 5.3.1](#), [5.3.2](#), and [5.4](#))
- Randomization

Provided that the subject fulfills all inclusion and no exclusion criteria, s/he will be randomized to treatment using the IVRS as described in [Section 6.3](#). Medication from the assigned treatment kit will be prepared as described in [Section 6.2](#) and administered i.a. according to instructions in the MOP.

- Using aseptic technique, i.a. administration of IMP will be guided by ultrasound to ensure delivery of the IMP into the joint space.
- Before injecting the IMP solution, an aspiration of the synovial fluid for PK and biomarker analysis will be performed as part of the i.a. injection procedure, using the same needle that

will be used for IMP injection. If possible, up to 2.5 mL of synovial fluid should be collected (instructions for sample handling are provided in the MOP).

If it is not possible to schedule an MRI scan for the same day as the other baseline assessments (including confirmation of eligibility by baseline WOMAC) for logistical reasons, the baseline MRI may be performed up to 3 days after confirmation of eligibility. Randomization and IMP administration will then take place on the day of the baseline MRI (following the scan), and subsequent visits will be planned relative to the day of randomization and IMP administration.

If confirmation of eligibility and baseline MRI scanning are performed on different days, all assessments of symptoms (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, NRS pain score in the target and contralateral knee, MOS SF-36, pain in other joints, and ICOAP) must be performed on the day of eligibility confirmation and all safety assessments and laboratory sampling must be performed on the day of MRI scanning (at appropriate times relative to IMP administration). Details of the division of procedures between these days are provided in [Appendix E](#).

7.1.3.2 IMP Administration

Subsequent IMP injections will be given at the following time points:

- Cycle 1: Weeks 1 and 2 (Visits 3 and 4)
- Cycle 2: Weeks 26, 27, and 28 (Visits 7, 8, and 9)
- Cycle 3: Weeks 52, 53, and 54 (Visits 12, 13, and 14)
- Cycle 4: Weeks 78, 79, and 80 (Visits 17, 18, and 19).

At visits where IMP is administered, all procedures should be performed before dosing unless otherwise specified. Urine pregnancy testing will be conducted in women of childbearing potential prior to each injection.

Immediately prior to dosing at each of these visits, the Investigator or delegate will obtain a blinded treatment kit number from the IVRS as described in Section 6.3. Medication from the assigned treatment kit will be prepared as described in Section 6.2 and administered i.a. according to instructions in the MOP.

- Using aseptic technique, i.a. administration will be guided by ultrasound to ensure delivery of the IMP into the joint space.
- Before injecting the IMP solution, an aspiration of the synovial fluid for PK and biomarker analysis will be performed as part of the i.a. injection procedure, using the same needle that will be used for injection. If possible, up to 2.5 mL should be collected (instructions for sample handling are provided in the MOP).

At visits where samples are collected for PK analyses (see [Appendix E](#)), subjects will be requested to stay in the study site for approximately 2 hours post-injection for collection of the

post-dose samples. At visits where biomarkers are collected, samples will be collected in the fasting state.

7.1.3.3 Major Efficacy Visits (Weeks 26, 52, 78, and 104; Visits 7, 12, 17, and 22)

Major efficacy visits will take place at intervals of 6 months (on the first day of each treatment cycle) and then at the end of the DBPC treatment phase (Week 104/Visit 22).

The following procedures will be performed at major efficacy visits. At visits where IMP is administered, all procedures should be performed before dosing unless otherwise specified. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score in the target and contralateral knee, MOS SF-36, pain in other joints, and ICOAP) should be completed before any other procedures are performed; the WOMAC should be completed first.

- WOMAC (see [Appendix C](#))
- PGA (see Section [7.3.3](#))
- KOOS QOL (see [Appendix D](#))
- KOOS Symptom Index (see [Appendix D](#))
- PGIC (see Section [7.7.4](#))
- NRS pain (see Section [7.7.5](#))
- Pain in other joints (see [Appendix F](#))
- MOS SF-36 (see [Appendix C](#))
- ICOAP (see [Appendix C](#))
- Review of AEs, concomitant medications, and concomitant procedures on the target knee (see Sections [7.4.1](#) and [6.5](#))
- Review of subject diaries (see Section [7.1.1](#))
- Vital signs measurement (see Section [7.4.4](#)),
- Physical examination including weight measurement (and height at Visit 22 only)
- Sample collection for hematology, biochemistry, and urinalysis (see Section [7.4.3](#) and [Appendix B](#))
- Blood collection for testing for antibodies to sprifermin/FGF-18 (see Section [7.4.3](#))
- Urine pregnancy test for women of childbearing potential
- 20-meter walk test (see Section [7.3.5](#))
- Target knee MRI (see Section [7.3.1](#))

- Knee X-ray (Weeks 52 and 104/Visits 12 and 22 only; see Section 7.3.4). An X-ray of the contralateral knee will be taken at Week 104/Visit 22.

IMP dosing and synovial fluid collection will take place at the following major efficacy visits: Weeks 26, 52, and 78/Visits 7, 12, and 17 (see Section 7.1.3.2).

7.1.3.4 Minor Efficacy Visits (Weeks 12, 38, 64, and 90; Visits 6, 11, 16, and 21)

Minor efficacy visits will take place at intervals of 6 months (12 weeks after the beginning of each treatment cycle).

The following procedures will be performed at these visits. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score in the target and contralateral knee, and ICOAP) should be completed before any other procedures are performed.

- WOMAC (see [Appendix C](#))
- PGA (see Section 7.3.3)
- KOOS QOL (see [Appendix D](#))
- KOOS Symptom Index (see [Appendix D](#))
- PGIC (see Section 7.7.4)
- NRS pain (see Section 7.7.5)
- ICOAP (see [Appendix C](#))
- Review of AEs, concomitant medications, and concomitant procedures on the target knee (see Sections 7.4.1 and 6.5)
- Review of subject diaries (see Section 7.1.1)
- Vital signs measurement (see Section 7.4.4)
- Physical examination
- 20-meter walk test (see Section 7.3.5)

7.1.4 Extended Follow-Up Phase

Visits during the 3-year extended follow-up phase will take place at 6-month intervals (see [Appendix E](#)). Subjects will be requested to discontinue the intake of all pain medications for 5 half-lives before each extended follow-up visit. At least 3 days before each visit, site staff will contact subjects by phone to remind them of this requirement.

The following procedures will be performed at all extended follow-up visits. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS pain score in the target and contralateral knee, pain in other joints, and ICOAP) should be completed before any other procedures are performed; the WOMAC should be completed first.

- WOMAC (see [Appendix C](#))
- PGA (see Section 7.3.3)
- KOOS QOL (see [Appendix D](#))
- KOOS Symptom Index
- PGIC (see Section 7.7.4)
- NRS pain (see Section 7.7.5)
- Pain in other joints (see [Appendix F](#))
- MOS SF-36 (see [Appendix C](#))
- ICOAP (see [Appendix C](#))
- Review of AEs, concomitant medications, and concomitant procedures on the target knee (see Sections 7.4.1 and 6.5)
- Review of subject diaries (see Section 7.1.1)
- Vital signs measurement (see Section 7.4.4)
- Physical examination including weight measurement
- Sample collection for hematology, biochemistry, and urinalysis (see Section 7.4.3 and [Appendix B](#))
- 20-meter walk test (see Section 7.3.5)

The following additional procedures will be performed at Extended Follow-up Visits 2, 4, and 6 (Weeks 156, 208, and 260/Visits 24, 26, and 28; i.e., at yearly intervals):

- Urine pregnancy test for women of childbearing potential (before performing X-ray and MRI)
- Target knee MRI (see Section 7.3.1)
- Knee X-ray (see Section 7.3.4). An X-ray of the contralateral knee will be taken at the final extended follow-up visit.
- Height will be measured at the final extended follow-up visit.

At each visit (with the exception of the final extended follow-up visit), subjects will be given trial diaries for recording of any AEs occurring or concomitant medications used between visits (see Section 7.1.1). Diaries will be collected and reviewed at the following visit.

7.1.5 Follow-Up in Case of Early Termination

Early Treatment Discontinuation

Subjects who discontinue treatment prematurely will undergo the assessments planned for Week 104/Visit 22 at the time of discontinuation (see [Appendix E](#)). If they are willing to continue in the trial, they will undergo all subsequent assessments planned for the remainder of their trial

participation (Visit 23 through Visit 28; with no further administration of IMP). Subjects who discontinue participation during the extended follow-up phase should have Week 260/Visit 28 procedures completed whenever possible.

Early Trial Withdrawal

Subjects who withdraw from the trial should undergo the assessments planned for Week 104/Visit 22 at the time of withdrawal whenever possible (see [Appendix E](#)).

7.2 Demographic and Other Baseline Characteristics

The demographic variables to be documented will be the subject identifier (to be assigned by the IVRS), age, sex, race, weight and height. Weight will also be measured every six months and height will be measured at the end of the DBPC and extended follow-up phases.

A complete medical history should be taken, covering all organ systems, diagnoses so far established, medications prescribed (including any vitamins and nutritional supplements taken), and surgical interventions performed. The medical history should also cover aspects such as allergies, consumption of alcohol, and smoking habits. Particular attention should be given to conditions potentially affecting trial eligibility.

Concerning concomitant treatments, particular attention should be given to the subject's use of NSAIDs, coxibs, and analgesics in general. These medications must be painstakingly recorded at baseline, as this information is needed for determination of eligibility for the trial. It will also be important to carefully record concomitant medication use throughout the trial.

A complete physical exam should also be performed, as detailed in the MOP.

Concerning the diagnosis of knee OA, it should be established for how long the disease has persisted and how it has been treated.

The target knee that will be treated with the IMP will be selected during the screening period. In case of bilateral OA, the more symptomatic knee should be chosen as the target knee.

7.3 Assessment of Efficacy

Assessment of efficacy in this trial will focus on MRI evaluation of treatment effect on knee cartilage. Effects of treatment on OA symptoms and functional limitations will be explored using the WOMAC questionnaire, the PGA, and the 20-meter walk test. The recognized endpoint of JSW measured by X-ray will also be used. These assessments are described in the sections below.

Exploratory analysis of treatment effect on health-related QOL will be performed using the KOOS QOL and the MOS SF-36 questionnaire. The NRS will be used to explore treatment effect on worst pain in the past 24 hours in the target knee. The ICOAP and the KOOS Symptom Index questionnaires will be used to explore the effect of treatment on OA-related symptomatology in the target knee. The NRS pain scale for the contralateral knee and a scale

model of the human body identifying potentially painful joints will be used to assess pain in non-target joints and the progression of OA. The PGIC will be used to measure the subject's assessment of the clinical importance of their improvement or worsening over the course of the trial. See Section 7.7 for description of these assessments.

The OMERACT-OARSI responder rate ((1); see Section 8.3.4) at 2 years will also be determined as an exploratory analysis, based on assessment of pain and function using the WOMAC and the PGA described in Section 7.3.3.

The rationale for the selection of efficacy measures and the timing of assessments is presented in Section 5.2.

7.3.1 Magnetic Resonance Imaging

MRI Scanning

MRI scanning will be performed using a high-resolution, 3-dimensional MRI machine with a commercially available dedicated knee coil. A 1.5 Tesla machine should be used.

It is recommended that machines from the same manufacturer be used to scan a given subject throughout the trial.

The scanning procedure is detailed in the MOP.

MRI Analysis

The trial's MRI endpoints will be addressed through quantitative MRI assessment of cartilage thickness and volume and semi-quantitative MRI assessment of cartilage structure.

MRI scans will be read centrally.

Quantitative MRI Assessment

OA is characterized by a progressive loss of cartilage that can be quantified by MRI. MRI is believed to detect structural changes faster than X-ray, although only JSW as measured by X-ray is accepted as a primary structural endpoint in confirmatory OA trials. For the purpose of quantification, the joint is divided into different compartments that may be more or less affected by OA. Quantitative MRI analysis in this trial will focus on the total knee and on the lateral and medial femorotibial compartments (LFTC and MFTC, respectively).

Quantitative MRI analysis for this trial will be performed under the direction of PPD [REDACTED].

Semi-quantitative MRI Assessment

Semi-quantitative assessment of the target knee will be performed using the Whole Organ Magnetic Resonance Imaging Score (WORMS (18)) and the Boston-Leeds Osteoarthritis Knee Score (BLOKS (24),(25)).

The WOMMS permits whole-organ assessment of the knee in OA based on conventional MRI images, and inter-observer agreement is high among trained readers. In its complete form, WOMMS incorporates assessment of 14 features: articular cartilage integrity (signal and morphology), subarticular bone marrow abnormality (bone marrow edema), subarticular cysts, subarticular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion, intra-articular loose bodies, and periarticular cysts/bursitis.

The BLOKS scoring method assesses 9 intra-articular regions and contains 8 items, including features of bone marrow lesions, cartilage, osteophytes, synovitis, effusions and ligaments. Possible scores for each feature range from 0 to 3. Maximal bone marrow lesion size using the BLOKS has been shown to have a positive linear relation with VAS pain, while this has not been demonstrated for the WOMMS.

Semi-quantitative MRI analysis for this trial will be performed and centrally analyzed as described in the Manual of Procedures (MOP).

7.3.2 WOMAC Questionnaire

The self-administered 24-question WOMAC Version 3.1 ((26); see [Appendix C](#)) will be used to assess pain, disability, and joint stiffness in the knee.

Subjects will answer all of the 24 questions themselves, using an 11-box numerical rating scale (with categories of 0 to 10), with reference to the past 48 hours. Different forms of the questionnaire exist for the right and the left knees: in order to reduce confounding of WOMAC responses by symptoms in the contralateral knee, subjects will use the WOMAC questionnaire specific to the target knee.

For administration of the questionnaire, instructions for the WOMAC 3.1 Index should be followed.

The WOMAC is widely used in clinical trials in hip and knee OA, and has been extensively validated. Appropriate validated translations will be used in each participating country.

The questionnaire addresses the degree of pain experienced with different activities or positions (5 questions), the degree and timing of joint stiffness (2 questions), and the degree of difficulty experienced in performing daily activities (17 questions). The maximum possible total score, indicating the worst possible OA symptoms, is 240 points. For convenience and ease of interpretation, all scores will be normalized on scales of 0 to 100 points.

The minimum clinically important difference in WOMAC scores is considered to be about 10% of the maximum possible score (27).

7.3.3 Patient's Global Assessment

In the Patient's Global Assessment (PGA) used in this trial, subjects will be asked to answer the following question using an 11-box numerical rating scale:

“Considering all the ways your osteoarthritis of the knee has affected you during the last 48 hours, circle the number that best describes the impact of your knee osteoarthritis on your daily life.”

0	1	2	3	4	5	6	7	8	9	10
None Extreme										

7.3.4 X-Ray Imaging

X-Ray Image Acquisition

Fixed flexion radiography will be used for the measurement of JSW. For the posterior-anterior projection of the target knee, the distance between focus and film will be equivalent to 183 cm (72 inches), and subjects must be positioned with their knees flexed at an angle of 20-30 degrees and their feet rotated internally at an angle of 10 degrees. Foot maps and a standardized radiological protocol will be used.

During the screening period, at the end of the DBPC treatment phase, and at the end of the extended follow-up phase, X-rays of both the target knee and the contralateral knee will be performed. At other time points, X-rays will be performed for the target knee only. A long-axis view of the target knee will also be obtained during screening to permit evaluation of malalignment.

Details are provided in the MOP.

X-Ray Image Analysis

X-rays will be read centrally.

X-ray images will be used to measure JSW in the medial and lateral femorotibial compartments and to determine the subject's baseline Kellgren-Lawrence grade.

Measurement of Joint Space Width

Change in JSW as measured by X-ray is a recognized endpoint accepted by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for use in efficacy trials in OA.

JSW will be measured using standardized technique that is described in the MOP.

Kellgren-Lawrence Scoring

The Kellgren-Lawrence (K-L) scale (28),(29) assigns severity grades for knee OA based on radiological assessment of the femorotibial joint (it is important to note that only the femorotibial joint is considered). A number from 0 to 4 is assigned, as follows:

- Grade 0: No feature of osteoarthritis
- Grade 1: Doubtful narrowing of joint space and possible osteophytic lipping
- Grade 2: Definite osteophytes and possible narrowing of joint space
- Grade 3: Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
- Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Kellgren-Lawrence scoring will be performed by the trial's imaging provider.

7.3.5 20-Meter Walk Test

The 20-meter walk test is an objective test of physical function which consists of measuring the time needed for the subject to walk 20 meters at a normal pace (30),(31). A stopwatch will be used for time measurement.

7.4 Assessment of Safety

The safety profile of sprifermin will be assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, physical examination findings including vital signs, weight, laboratory tests, and incidence of surgical interventions in the target knee (including any surgical revision, cartilage removal, operation, or any other type of surgical intervention).

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the Investigator or reported by the subject (see Section 7.4.1.4, "Methods of Recording and Assessing Adverse Events").

The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

The Investigator is required to grade the severity of each AE.

Investigators must assess the severity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

Investigators must also systematically assess the causal relationship of AEs to the IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of the IMP, medical history, concomitant medication, course of the underlying disease, and trial procedures.

Not related: Not suspected to be reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.

NOTE: The term “life-threatening” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner as described in Section [7.4.1.4](#).

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs.

Progression of underlying disease is not an AE and therefore not an SAE per se, rather an efficacy endpoint, unless deemed to be causally related to IMP administration.

Pre-defined AEs of Special Interest for Safety Monitoring

One of the trial’s safety endpoints is the incidence of AIRs, defined as increase of pain by 30 mm on a 100-mm VAS and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection.

It is recognized that events meeting this definition will not be necessarily drug-related or inflammatory in nature; however, it is believed that the definition will permit capture of most clinically relevant local reactions. A similar definition based on a 30-mm increase in pain and local swelling was used in a trial in rheumatoid arthritis involving i.a. injections of interleukin-1 receptor antagonist (IL-1ra; anakinra (23)).

At each visit, subjects will be given trial diaries for recording of any AEs occurring or concomitant medications used between visits. These diaries will also be used to record maximum pain (using a 100-mm VAS) and presence or absence of joint swelling in the target knee for the day before and the 3 days after each IMP injection (see Section 7.1.1).

Completed diaries will be collected and reviewed at each visit, and information will be transcribed to the CRFs following medical review. AIRs will be identified by the Sponsor based on the information about pain and swelling that is transcribed from the diaries to the CRFs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period of the trial, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Subjects will be asked to record information about any adverse reactions experienced between trial visits on their trial diaries (see Section 7.1.1). Diaries will be reviewed at each trial visit; information thus collected will be reviewed and assessed medically before it is transcribed to the CRF.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. Among these AEs, all serious AEs must be additionally documented and reported using an Adverse Event Safety Report Form (Clinical Trial) as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates (and times, if relevant)), its severity, its relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP), and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Because of the i.a. route of administration used and the expectation that the great majority of the injected drug will remain within the knee joint, Investigators must classify each reported AE as "local (i.e., concerning only the knee that is treated)" or "systemic" in the subject's CRF to permit separate evaluation of AEs classified as local and AEs classified as systemic.

Specific guidance can be found in the CRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues until the end of the trial's post-treatment extended follow-up phase, or until the subject's final trial visit in case of early withdrawal.

7.4.1.4 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (i.e., within a maximum 24 HOURS after becoming aware of the event) inform the Sponsor's GDS department by fax or by e-mail.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (i.e., follow-up).

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the Adverse Event Safety Report Form (Clinical Trials).

All written reports should be transmitted using the Adverse Event Safety Report Form (Clinical Trials), which must be completed by the Investigator following specific completion instructions.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant medications). In all cases, the information provided in the Adverse Event Safety Report Form (Clinical Trials) must be consistent with the data on the event that are recorded in the corresponding sections of the CRF.

The Investigator/Reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible Monitor, although in exceptional circumstances the GDS department may contact the Investigator directly to obtain clarification or to discuss a particularly critical event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of “findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC’s/IRB’s approval/favorable opinion to continue the trial.” In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (“suspected unexpected serious adverse reactions” or SUSARs). The Investigator should place copies of Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor’s responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidances.

7.4.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical trial and is considered to be possibly related to the IMP must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. The Sponsor will actively follow up and collect information on any AE that occurs during the course of a clinical trial; however, while this activity will continue for any serious AEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the CRF. The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the Adverse Event Safety Report Form (Clinical Trials) when

the subject sustains an event, and the Parent-Child/Fetus Adverse Event Report Form when the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Laboratory Assessments

Standard laboratory assessments in this trial will consist of hematology, clinical biochemistry, and urinalysis panels: complete lists of parameters are presented in [Appendix B](#).

As an exogenous protein, sprifermin has the potential to trigger antibody formation, which could conceivably have safety, PK, or efficacy implications. Thus, subjects will be tested for binding and neutralizing antibodies to sprifermin/FGF-18. Only samples that are found to be positive for binding antibodies will be tested for neutralizing antibodies.

Blood, urine, and synovial fluid samples for laboratory assessment will be collected at the time points indicated in [Appendix E](#).

- Subjects are not required to fast before routine laboratory sample collection in this protocol, however, an 8-hour fast is required before blood or urine sample collection for biomarkers.
- For time points where IMP injections are administered, blood and urine samples will be collected pre-dose.
- For measurement of biomarkers in urine, second morning void samples should be obtained.
- Synovial fluid samples will be collected immediately before injection of the IMP as described in the MOP.

PK assessments are described in Section 7.5, and biomarker and PGt assessments are described in Section 7.6.

All laboratory assessments will be performed centrally. Instructions for sample collection, handling, and shipment are provided in the MOP.

Pregnancy Tests

For women of childbearing potential, pregnancy tests will be performed at the time points shown in [Appendix E](#) (during screening, before each injection of IMP, and at each visit involving X-ray and MRI). A serum test will be performed during screening, and urine tests will be performed at subsequent time points.

Management of Subjects with Laboratory Abnormalities

Laboratory abnormalities that Investigators consider to be clinically significant should be reported as AEs (see Section 7.4.1).

The best interest of the participating subject will always come before that of the trial. Abnormalities of any safety laboratory analysis considered to represent a significant danger to the subject will lead to immediate discontinuation of the drug, and the Medical Responsible must be informed immediately.

In the event of significant abnormalities considered not to represent a danger, continuation of the drug may be allowed after discussion with the Medical Responsible. These subjects will be followed up with appropriate medical management until there is a return to normal or baseline values, or until a clinical diagnosis of a trial-emergent illness is confirmed.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Physical examinations and measurement of height, weight, and vital signs (sitting systolic and diastolic blood pressure, heart rate, and body temperature) will be performed at the time points specified in [Appendix E](#).

Standard 12-lead ECGs (reporting ventricular rate, PR, QRS, QT, and QTc intervals) will be obtained at the time points specified in [Appendix E](#). ECGs will be read centrally; procedures for transfer of data to the central reader are provided in the MOP. Original 12-lead ECG tracings will be retained in each individual subject's medical file. In case of abnormal results, a second original will be provided to the Sponsor. ECGs can be repeated at the discretion of the Investigator or co-Investigator.

One of the trial's safety endpoints is the incidence of AIRs, defined as increase of pain by 30 mm on a 100-mm VAS and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection (see Section 7.4.1.1). Subjects will use trial diaries to record maximum levels of target knee pain experienced, using a 100-mm VAS, and presence or absence of joint swelling in the target knee. Completed diaries will be collected and reviewed at each visit, and information will be transcribed to the CRFs following medical review. AIRs will be identified by the Sponsor based on the information about pain and swelling transcribed from the diaries to the CRFs.

7.5 Pharmacokinetics

PK assessment will be performed for sprifermin/FGF-18 in serum and synovial fluid.

Sprifermin differs from the endogenous FGF-18 molecule in that it is truncated (i.e., it has 170 instead of 180 amino acids), it has a methionine extension, and it is not glycosylated.

Merck Serono internal Standard Operating Procedure HP01 describes the process for handling bioanalytical, PK, and pharmacodynamic (PD) data from double-blind clinical trials. To maintain

the blind for PK data during this trial, the randomization list will only be provided to the PK bioanalytical scientist or clinical trial team members after clinical database lock.

7.5.1 Body Fluids

Blood and synovial fluid samples for measurement of serum/synovial fluid sprifermin/FGF-18 levels will be collected at the time points indicated in the schedule of assessments in [Appendix E](#).

Detailed description of sample preparation, labels, and shipments will be given in the MOP. Details of the assays such as the validation procedure and definition of lower limit of quantification (LLOQ) will be described by the Sponsor/external laboratory in a separate analytical protocol. Some samples might be stored and used for additional analysis or for validation of new assays.

- Blood samples for the measurement of sprifermin/FGF-18 serum levels will be collected at pre-dose at Week 0 and thereafter at 2 hours after the last dose of each cycle.
- Synovial fluid for the measurement of sprifermin/FGF-18 levels will be aspirated under ultrasound guidance (32) prior to i.a. injection of sprifermin, as part of the i.a. injection procedure and using the same needle that will be used for IMP injection, as described in the MOP.

7.5.2 Pharmacokinetic Calculations

The PK analysis will be performed under the responsibility of the Sponsor according to the Sponsor's appropriate standard operating procedures. Sprifermin/FGF-18 serum and synovial fluid concentrations will be summarized at the time points shown in [Appendix E](#). Details of the analysis and data displays will be provided in the Statistical Analysis Plan (SAP). Analytes to be tested in this study will include serum and synovial fluid sprifermin/FGF-18.

7.6 Biomarkers and Pharmacogenetics

Circulating biomarkers will be assessed for all subjects in serum, urine, and (if sample volumes permit) synovial fluid. Exploratory PGt analyses will be performed only for subjects who provide separate informed consent.

7.6.1 Biomarkers to be Analyzed

Serological and urine biochemical markers of bone and joint tissue turnover will be evaluated. Potential biomarkers may include, but are not limited to: aggrecan chondroitin sulfate epitope 846 (CS846), II form of the propeptides from the N- terminus processed type II collagen (PIINP), propeptides from the C-terminus processed type II collagen (PIICP), and C-telopeptide cross-linking of type II collagen (CTX-II).

Measurement of biomarkers in synovial fluid is also foreseen. However, if the quantity of synovial fluid collected is not sufficient to permit both PK and biomarker measurement, priority will be given to PK.

Samples will be stored for up to 5 years after trial completion under the Sponsor's responsibility. During this time, it is possible that the samples will be re-analyzed by the Sponsor or its designee. This may include analyses for newly identified markers and/or a repeat of the original analysis with newer improved technologies. After this period of 5 years, either the samples will be destroyed or fully anonymized or new IEC/IRB approval will be requested to keep them for an additional period.

7.6.2 Body Fluids for Biomarker Assessment

Blood and urine samples for systemic biomarker assessment will be collected at the time points specified in [Appendix E](#). For time points where IMP injections are administered, samples will be collected pre-dose. For urine collection, second morning void samples should be obtained.

Synovial fluid samples will be collected at the time points specified in [Appendix E](#). These samples will be taken just before injection of the IMP as described in the MOP, as part of the i.a. injection procedure and using the same needle that will be used for IMP injection. If sample volume permits, biomarkers will be analyzed in the samples collected at Week 0/Visit 2, Week 28/Visit 9, Week 54/Visit 14 and Week 80/Visit 19; otherwise, priority will be given to PK.

Instructions for the preparation and handling of blood samples for assessment of circulating proteins can be found in the MOP.

7.6.3 Pharmacogenetics

Exploratory analyses are planned to identify potential associations of genetic variations with safety events, drug response, and/or treatment efficacy.

All subjects who are enrolled in the trial will be eligible to participate in the optional PGt analysis (except in countries where collection of PGt samples is not allowed). Participation is optional, and the subjects who choose to participate will need to sign a specific PGt ICF (see [Section 9.2](#)).

The results of the genetic analysis are for research purposes only. The results of the genetic tests will not be made available to the subject, members of his/her family, his/her personal physician, or other third parties, except as specified in [Section 9.3](#).

Once a subject has given appropriate consent, a single blood sample for PGt analysis will be collected; this sample can be taken at any trial visit (including pre-dose at the baseline visit).

Instructions for the preparation and handling of blood samples for PGt analysis can be found in the MOP.

Samples will be stored for up to 5 years after trial completion under the Sponsor's responsibility. During this time, it is possible that the samples will be re-analyzed by the Sponsor or its designee. This may include analyses for newly identified markers and/or a repeat of the original analysis with newer improved technologies. After this period of 5 years, either samples will be destroyed or fully anonymized or new IEC/IRB approval to keep the samples for an additional period will be requested.

7.7 Other Assessments

7.7.1 Knee Injury and Osteoarthritis Outcome Score - Quality of Life and Symptom Index Subscales

The KOOS (33) is a knee-specific questionnaire designed to evaluate both short-term and long-term consequences of knee injury, including OA; it is intended for use in knee injury potentially leading to post-traumatic OA or in primary OA. It consists of 42 items grouped into 5 subscales: pain, other symptoms (including swelling, restricted range of motion, and mechanical symptoms), function in daily living (ADL), function in sport and recreation (i.e., impact on more demanding physical activities), and impact on quality of life (including awareness of the knee condition and changes in lifestyle). The subscales are scored separately; each yields a score between 0 and 100, with 0 representing extreme knee problems and 100 representing absence of problems. The 42 items of the complete KOOS include the 24 items of the WOMAC Osteoarthritis Index (26), the most frequently used patient-assessed measure of treatment effect in OA. In this study, there will be no duplication of questions from the WOMAC and the KOOS.

The KOOS has been validated for use in patients undergoing total knee replacement for OA. Content validity in this patient group was assessed before surgery by asking patients to rate the importance of improvement in each of the KOOS subscales. Notably, larger effect sizes were seen with the KOOS compared to the WOMAC following TKR for severe knee OA (33),(34). A change of 10 points in KOOS score has been proposed as representing clinically meaningful difference based on experience with the WOMAC; however, the minimal perceptible clinical improvement (MPCI; defined as the change in score associated with the smallest change in health status detectable by the patient) has not been formally assessed for the KOOS (33).

In this trial, the KOOS quality of life subscale will be evaluated at the same time points as the WOMAC, as a complement to the more general MOS SF-36 (see below). The KOOS Symptom Index will also be completed at the same time points for correlation with the other indicators of tibiofemoral cartilage loss (e.g., MRI, X-ray).

7.7.2 Medical Outcomes Study Short Form-36 General Health Survey

The MOS SF-36 (version 2.0) is a multi-purpose questionnaire that measures general health status and QOL, is not knee specific, and is the single PRO measure included to assess the overall status of the patient. It consists of 36 items that evaluate 8 dimensions of health: physical function, bodily pain, general mental health, vitality (energy and fatigue), social function, physical role (role limitations due to physical health), emotional role (role limitations due to

personal or emotional problems), and general health perceptions. Scores for the 8 dimensions/subscales range from 0 to 100, with higher scores representing better QOL. The MOS SF-36 is a generic measure as opposed to one targeting a specific age group, disease, or treatment. Accordingly, it has proven useful in surveys of general and specific populations, comparing the relative burden of different diseases, and examining the health benefits associated with a wide range of treatments. It should be noted that there is no defined MOS SF-36 score that represents a healthy, unimpaired condition. A subject with no disease symptoms would not necessarily have subscale scores of 100 or corresponding physical, mental, and summary scores of 400 or 800.

According to the User's Manual for the MOS SF-36 v. 2.0 Health Survey and Kosinski et al. (35), "minimal important differences" in MOS SF-36 scores consist of changes of 2 to 4 points, depending on the subscale concerned.

7.7.3 Measure of Intermittent and Constant Osteoarthritis Pain Questionnaire

The ICOAP (36),(37),(38) is an 11-item questionnaire for assessment of pain in subjects with OA that considers both constant and intermittent experiences of pain. Questions address the frequency and severity of pain and its impact on the subject's QOL (including sleep and emotional distress).

The ICOAP is designed to be responsive to change in pain over time and with treatment. Subjects are asked to respond to the questionnaire considering their symptoms over the past week, taking into consideration any pain medication that they may be using (i.e., to report their experience of pain while taking the medication).

The ICOAP yields a total pain score that can range from 0 to 44 points, a constant pain subscore that can range from 0 to 20 points, and an intermittent pain subscore that can range from 0 to 24 points; higher scores indicate more severe, frequent, or distressing pain.

7.7.4 Patient Global Impression of Change

Global impression scales (39) are recommended for use in chronic pain clinical trials as a core outcome measure of global improvement with treatment relative to baseline symptoms (40). It provides a responsive and readily interpretable measure of participant's assessments of the clinical importance of their improvement or worsening over the course of the clinical trial.

The PGIC used in this trial is based on the IMMPACT recommendations (40) and will assess the subject's global improvement since starting study treatment using a 7-point scale:

“Since getting the first injection of study treatment in your knee how would you describe the change in overall symptoms for this knee:”

- 1 = very much improved
- 2 = much improved
- 3 = minimally improved
- 4 = no change
- 5 = minimally worse
- 6 = much worse
- 7 = very much worse

7.7.5 11-Point Numerical Rating Scale Pain Score

The subject will indicate the worst pain in past 24 hours in the target and contralateral knee using an 11-point NRS. The NRS for pain is a patient-reported unidimensional pain scale recommended for assessing pain intensity (41) which is frequently used instrument in pain trials, and also in subjects with osteoarthritis.

The NRS is scaled from 0 (no pain) to 10 (worst possible pain). It has good validity, reliability, and sensitivity, being similar in sensitivity to a 100-mm VAS when comparing postoperative pain intensity (42).

In this protocol, the NRS will be used as a supplementary pain scale to the WOMAC. The NRS has a 24-hour recall period, which may be preferable for detecting recent changes in health status compared to PRO questionnaires with longer recall periods (43). Also, the NRS involves a single overall question whereas the WOMAC uses a group questions to characterize different aspects of knee pain.

7.7.6 Pain in Other Joints

Data on the presence of pain in ‘other’ joints (that is, joints other than the knee) will be obtained because, like pain in the contralateral knee, pain in other joints could potentially become a confounding variable when assessing self-reported activities of daily living (WOMAC ADL), physical functioning during the 20-meter walk test, and overall health-related quality of life (MOS SF-36). Pain in other joints may also serve as indicator of overall OA progression. As has been recommended for use in OA studies (44), a scale model of the human body (homunculus) will be used (see Appendix F). During subject interview, the homunculus, with circles in six bilateral joints (shoulder, elbow, wrist, hand/finger, ankle, foot) and neck, for a total of 13 joints, will be shown to subjects to indicate painful joints.

8 Statistics

8.1 Sample Size

The sample size was determined from expected changes in the primary endpoint: the change from baseline in cartilage thickness in the total femorotibial joint as evaluated by MRI at 2 years.

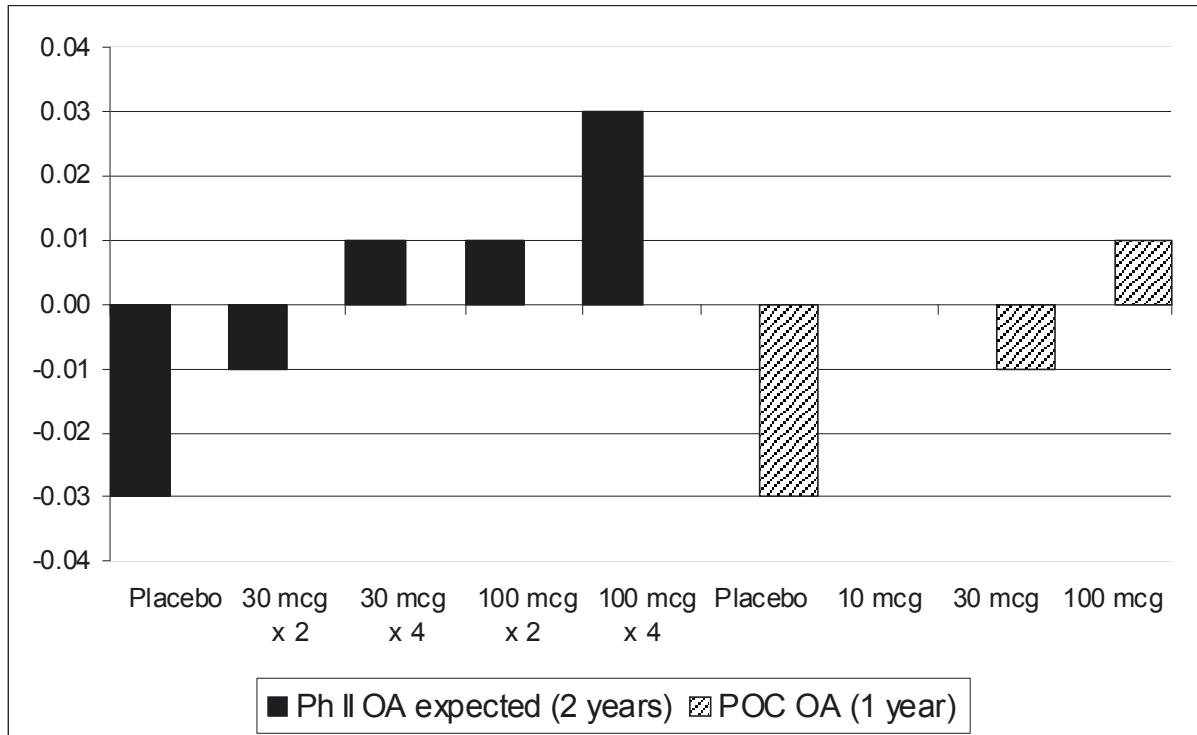
This trial is set up to detect a potential dose relationship, based on the total dose of sprifermin received over the 2 years, in limiting the reduction of or increasing the cartilage thickness in the total femorotibial joint, assuming:

- A mean change from baseline at 2 years of
 - -0.03 mm in the placebo group (i.e., 0 mcg over 2 years)
 - -0.01 mm in the sprifermin 30 mcg once a year group (i.e., 180 mcg over 2 years)
 - +0.01 mm in the sprifermin 30 mcg twice a year group (i.e., 360 mcg over 2 years)
 - +0.01 mm in the sprifermin 100 mcg once a year group (i.e., 600 mcg over 2 years)
 - +0.03 mm in the sprifermin 100 mcg twice a year group (i.e., 1200 mcg over 2 years)
- A common SD (standard deviation) of 0.10 mm
- A type-one error, α , of the primary efficacy analysis set at 5% two-sided
- Normal distribution.

The above assumptions were based on available MRI data from the OAI (<http://oai.epi-ucsf.org/datarelease/>) and from the POC trial (28980; see [Figure 3](#)).

A minor deviation from linearity has been introduced in these hypotheses based on the expectation of similar changes for the sprifermin 30 mcg twice a year and sprifermin 100 mcg once a year groups. Indeed, according to the current knowledge of the biological mechanism of action of sprifermin, the treatment effect of the highest dose (100 mcg) given once a year could be similar to that of a lower dose (30 mcg) given twice a year. Moreover, the variability of the measure is large, and therefore a deviation from perfect linearity may be expected.

Figure 3 **Expected Mean Changes in Cartilage Thickness (mm) in Total Knee at 2 Years (SD = 0.10)**



OA: osteoarthritis; POC: proof of concept; SD: standard deviation

Calculations showed that:

- 55 evaluable subjects in each group (total 275 subjects) will ensure a power of 90% for detecting a linear dose relationship using a linear trend test,
- 76 evaluable subjects in each group (total 380 subjects) will ensure a power of 90% for detecting an overall treatment effect (meaning that at least one group differs from the other groups) as well.

Based on recent literature and other trial experience (45, 46), the subject discontinuation rate is estimated to be close to 30% at two years. Assuming a 30% drop-out rate, a total of 545 subjects should be randomized (109 subjects per group) in order to detect an overall treatment effect.

In order to be able to demonstrate that structure improvement translates into symptomatic benefit, it is important that the study be adequately powered to detect significant differences in normalized WOMAC scores. With 76 evaluable subjects per treatment group, the power to show a statistically significant difference between at least one active treatment group and the placebo group for the secondary WOMAC endpoints ranges from 69% to 87% for the total score, from 80% to 99% for the pain score and from 53% to 83% for the function score, depending on the expected mean difference from placebo (see Table 3).

Table 3 Power Calculations for Pairwise Differences (Sprifermin versus Placebo) on Normalized WOMAC Scores with 76 Evaluable Subjects per Treatment Group

	Expected mean difference from Placebo	Common SD	Power
Total Score - Normalized (range 0-100 points)	8 points	20	69%
	9 points		79%
	10 points		87%
Pain Score - Normalized (range 0-100 points)	10 points	22	80%
	15 points		99%
Function Score - Normalized (range 0-100 points)	7 points	21	53%
	9 points		75%
	10 points		83%

SD: standard deviation; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

For reference, a difference of 10 points from placebo in the normalized WOMAC scores is considered as clinically meaningful (highlighted in bold type in the table).

8.2 Randomization

Randomization will be coordinated centrally, using an IVRS system which will allocate subjects to the treatment groups (see Section 6.3 for further details concerning the technical and logistical aspects of treatment allocation).

Eligible subjects will be randomized to one of the 5 treatment groups with an allocation ratio of 1:1:1:1:1, using a computer-generated randomization list in random permuted blocks.

Randomization will be stratified by country to ensure balance of treatment groups with respect to intrinsic and extrinsic factors that may affect OA outcomes. Moreover, it may not be practical to stratify randomization by site as numbers of subjects in each site are expected to be small.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint of this trial is the change from baseline in cartilage thickness in the total femorotibial joint as evaluated by MRI at 2 years.

8.3.2 Secondary Endpoints

Secondary efficacy endpoints are:

- Changes from baseline in the WOMAC total score and in the WOMAC pain, function, and stiffness index scores over 2 years
- Change from baseline in the 20-meter walk test over 2 years

- Change from baseline in the PGA over 2 years
- Change from baseline in minimal JSW in the medial and lateral compartments as evaluated by X-ray over 2 years
- Change from baseline in cartilage thickness in the medial and lateral compartments as well as in the total femorotibial joint over 2 years
- Change from baseline in cartilage volume in the medial and lateral compartments as well as in the total femorotibial joint over 2 years
- Synovial fluid levels of sprifermin/FGF-18
- Serum levels of sprifermin/FGF-18

8.3.3 Safety Endpoints

Safety endpoints are:

- Nature, incidence and severity of local and systemic AEs
- Incidence of acute inflammatory reactions (AIRs), defined as increase of pain by 30 mm on a 100 mm VAS associated with a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection
- Changes in laboratory safety parameters, vital signs, 12-lead ECG parameters, weight, and physical examinations
- Incidence of surgical interventions in the target knee (including any surgical revision, cartilage removal, or any other type of surgical intervention)
- Occurrence of binding and neutralizing antibodies to sprifermin/FGF-18

8.3.4 Exploratory Endpoints

Exploratory endpoints are:

- Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate (1) at 2 years
- PGIC over 2 years
- Changes from baseline in the scores of the KOOS QOL and the MOS SF-36 questionnaire over 2 years
- Change from baseline in KOOS Symptom Index over 2 years
- Change from baseline in pain score in the target and contralateral knee over 2 years using an 11-point NRS
- Change from baseline in presence of pain in other joints over 2 years
- Change from baseline in ICOAP scores over 2 years

- Change over time in structural as well as compositional parameters of the knee joint (e.g., synovium, menisci, bone, and other structures) as evaluated by MRI
- Change from baseline in serum, urine, and synovial markers associated with administration of the compound
- Baseline protein markers and/or genetic markers associated with response to treatment or disease progression (response assessed by MRI and/or questionnaire)
- Changes in MRI outcomes, WOMAC scores, 20-meter walk test, PGA, PGIC, JSW, OMERACT-OARSI responder rate, KOOS QOL, KOOS Symptom Index, MOS SF-36, NRS pain score in the target and contralateral knee, presence of pain in other joints, ICOAP, safety laboratory values, and vital signs over the extended follow-up period and nature, incidence and severity of local and systemic AEs during the extended follow-up period (to be summarized descriptively)
- Relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time

The Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate (1) will be determined as an exploratory analysis. The OMERACT-OARSI responder criteria involve changes that are deemed to be clinically relevant in three domains: pain, function, and Patient’s Global Assessment. For each of these domains, ranges are defined for absolute and percent changes from baseline that correspond to “high improvement” and “moderate improvement”. OMERACT-OARSI response is defined as either i) high improvement in pain or function or ii) moderate improvement in at least 2 of the 3 domains (pain, function, and Patient’s Global Assessment).

In this trial, OMERACT-OARSI response will be determined using WOMAC pain and function index scores and the PGA described in Section 7.3.3.

8.4 Analysis Sets

Intention-to-Treat Analysis Set (Full Analysis Set)

The Intention-to-Treat (ITT) Analysis Set will include all subjects randomly allocated to a treatment, based on the intention to treat “as randomized” principle (i.e., the planned treatment regimen rather than the actual treatment given in case of any difference).

Modified Intention-to-Treat Analysis Set

The Modified ITT (mITT) Analysis Set will include all subjects from the ITT Analysis Set who have a baseline and at least one post-treatment MRI assessment available.

Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will include all subjects from the mITT Analysis Set who have been treated according to the clinical trial protocol and fulfill the following criteria:

- Compliance with all entry criteria
- Absence of major clinical trial protocol violations with respect to factors likely to affect the efficacy of treatment, where the nature of such clinical trial protocol violations will be defined before breaking the blind
- Adequate compliance with trial medication (this will be defined in the SAP)

Safety Analysis Set

The Safety Analysis Set will include all subjects who receive at least one dose of trial treatment. Subjects will be analyzed according to the actual treatment they receive.

Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects from the Safety Analysis Set with at least one available serum or synovial fluid measurement.

Subgroup Analyses

Subgroup analyses (especially for the analysis of the primary endpoint) will be considered for categories including Kellgren-Lawrence grade (Grade 2, Grade 3), sex (Male, Female), age (< 65 years old, \geq 65 years old), body mass index (BMI; < 30 kg/m², \geq 30 kg/m²), and country.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

An outline of the analysis currently planned is presented in the following sections. The full documentation will be provided in the Statistical Analysis Plan (SAP), which will be finalized before database lock and unblinding.

It is planned to perform the statistical analysis in two steps. Approximately three months after the last subject's last visit of the DBPC treatment phase, the database will be locked, the treatment code will be unblinded, complete analyses will be performed, and a detailed Clinical Trial Report will be written based on the data collected up to the end of the DBPC treatment phase. Long-term follow-up data will be analyzed and reported separately from the DBPC treatment phase results. MRI readers, Investigators, and subjects will remain blinded during the extended follow-up phase.

Summary Statistics

The summary statistics presented for quantitative variables will be the number of observations (n), the number of missing values (missing), mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), and minimum (min) and maximum (max) values.

The summary statistics presented for categorical data will be the number of observations (n), the number of missing values (missing), and the count and percentage of subjects in each category.

Adjustment for Multiplicity

The main objective of this Phase II trial is to select a dose regimen for further development in Phase III; therefore, no adjustment for multiplicity will be made. Caution should be used in interpreting significant p-values ($p < 0.05$). Interpretation of the results will involve global consideration of all efficacy results obtained in combination with an appropriate judgment of clinical significance.

Missing Data

As a general rule, all data collected and available will be used in the analysis. No imputation of missing data will be applied independently of the statistical method used to analyze the data.

Handling of missing data from questionnaires will depend on whether only single items are missing or a complete questionnaire is missing. If only single items are missing, the rules defined by the authors of the questionnaires (if any) will be followed. If a complete questionnaire is missing, different methods of imputation will be used and results will be compared in a sensitivity analysis.

8.5.2 Analysis of Primary Endpoint

The primary endpoint is the change from baseline in cartilage thickness in the total femorotibial joint as evaluated by MRI at 2 years.

The cartilage thickness in the total femorotibial joint as evaluated by MRI will be tabulated per time point (visit) and treatment group, along with the absolute change from baseline and the percent change from baseline.

The treatment effect on the primary endpoint will be assessed through dose-ranging using a repeated measurement analysis of variance (ANOVA, using PROC MIXED in SAS) on absolute change from baseline, including the baseline value, the treatment group, the time, and the country as factors and including treatment by time as interaction.

The primary efficacy analysis will consist of testing the linear dose relationship and the overall treatment effect at 2 years. The significance level will be set at 5% two-sided for both tests.

For the linear dose relationship testing, the null and alternative hypotheses will be:

$$H_0: -2 \text{ Mean}_{(\text{Placebo})} - 1 \text{ Mean}_{(180 \text{ mcg})} + 0 \text{ Mean}_{(360 \text{ mcg})} + 1 \text{ Mean}_{(600 \text{ mcg})} + 2 \text{ Mean}_{(1200 \text{ mcg})} = 0$$

$$H_1: -2 \text{ Mean}_{(\text{Placebo})} - 1 \text{ Mean}_{(180 \text{ mcg})} + 0 \text{ Mean}_{(360 \text{ mcg})} + 1 \text{ Mean}_{(600 \text{ mcg})} + 2 \text{ Mean}_{(1200 \text{ mcg})} \neq 0$$

where the doses shown are the total doses of sprifermin to be administered over the DBPC treatment phase (see [Table 1](#)).

If the null hypothesis is rejected, the alternative hypothesis will be accepted and it will be concluded that there is a dose relationship versus placebo over time.

For the overall treatment effect testing, the null and alternative hypotheses will be:

$$H_0: \text{Mean}_{(\text{Placebo})} = \text{Mean}_{(180 \text{ mcg})} = \text{Mean}_{(360 \text{ mcg})} = \text{Mean}_{(600 \text{ mcg})} = \text{Mean}_{(1200 \text{ mcg})}$$

$$H_1: \text{Mean}(i) \neq \text{Mean}(j) \text{ for some } i \neq j \text{ and } i, j = \text{Placebo or } 180 \text{ mcg or } 360 \text{ mcg or } 600 \text{ mcg or } 1200 \text{ mcg.}$$

where the doses shown are the total doses of sprifermin to be administered over the DBPC treatment phase (see [Table 1](#)).

If the null hypothesis is rejected, the alternative hypothesis will be accepted and it will be concluded that there is at least one group that differs from the other groups.

Pairwise comparisons (sprifermin versus placebo, and between sprifermin dose and regimen groups) will be performed within the context of this modeling framework. For each pairwise comparison, the difference between treatments and the corresponding 95% confidence interval (CI) and p-value will be presented.

The primary efficacy analysis will be performed on the mITT Analysis Set.

In order to assess the robustness of the primary results, sensitivity analyses will be performed with modification of subject population (PP Analysis Set), statistical methods (influence of the distribution, influence of the time effect, and so on), and influence of covariates.

8.5.3 Analysis of Secondary Endpoints

Descriptive statistics for secondary efficacy endpoints will be presented by time point (visit) and treatment group.

The same ANOVA model used for the primary endpoint will be used to assess the treatment effect on continuous secondary endpoints such as MRI endpoints, WOMAC endpoints (total, pain, function, and stiffness scores), and X-ray endpoints at each time point and over time.

Logistic regression will be used to assess the treatment effect on the binary efficacy endpoints such as the OMERACT-OARSI responder rate. Point estimates for each pairwise comparison and corresponding 95% CIs and p-values will be provided.

8.5.4 Safety Analyses

Safety data will be summarized descriptively overall and by treatment group, using the Safety Analysis Set.

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

All local and systemic AEs will be reported overall, by severity, and by relationship to trial drug, and summaries will be prepared of events leading to discontinuation and events leading to death.

The incidence of protocol-defined AIRs and the incidence of surgical procedures occurring to the target knee during the trial will be tabulated separately.

Laboratory safety parameters and vital signs will be descriptively summarized as appropriate.

8.5.5 Analysis of Further Endpoints

The following domains will be described overall and by treatment group using summary statistics:

- Disposition of subjects and discontinuations
- Protocol deviations
- Demographics, medical history, and other baseline characteristics
- Past and concomitant medications and procedures, with particular attention to pain medications
- Treatment compliance and exposure, as assessed by the number of injections received

PK sample bioanalysis will be performed by Merck Serono NCD-DMPK; and PK data analyses, as well as investigation of the relationship between dosing (dose and regimen), cartilage structure, and clinical scores as a function of time will be performed by Merck Serono Exploratory Medicine.

Exploratory biomarker sample and data analyses will be performed under the responsibility of Merck Serono NCD – Biomarker Technologies. The sample analytes will be further specified in the Manual of Procedures (MOP), and data analysis will be described in an Exploratory Biomarkers Statistical Analysis Plan (SAP). Results will be reported separately in an Exploratory Biomarkers Report.

Analysis of Data from the Extended Follow-up Phase

Data reported during the extended follow-up phase will be presented mainly using descriptive statistics.

Exploratory Pharmacometric Modeling

A modeling analysis will be performed in order to evaluate the disease-modifying effect of sprifermin, i.e., improvement of cartilage structure and clinical symptoms (WOMAC).

In particular, the relationship between cartilage structure changes and improvement of clinical symptoms will be investigated, in order to support the selection of the optimal dose/dosing regimen for future trials.

In order to derive a better understanding of sprifermin effects, other potential influencing/confounding factors such as the placebo effect will be included in the model.

The development of the models implies a covariate analysis to explore the influence of various potential predictors of variability, e.g., demographics/anthropometrics, biomarkers (including PGt markers), and concomitant medications.

Finally, simulations will be performed to address various scenarios, to support decision making and planning of future studies.

Additional models focusing on other secondary/exploratory endpoints could be developed if deemed appropriate.

The details of modeling and simulation analyses will be described in a Modeling and Simulation Data Analysis Plan.

8.6 Interim Analysis

No interim analysis is planned.

An IDMC will be constituted and will perform periodic reviews to evaluate the safety of the subjects participating in the trial on an ongoing basis. Detailed description of the safety monitoring will be specified in a dedicated IDMC charter.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. S/he will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In

particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

In 1998, the US Food and Drug Administration (FDA) introduced a regulation (21 CFR, Part 54) entitled “Financial Disclosure by Clinical Investigators”. For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP (named “covered trials” by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor’s product under study. This information is required during the trial and for 12 months following completion of the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject’s participation in the trial is his/her written informed consent. The subject’s written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by laypersons.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator’s site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject’s consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

Pharmacogenetics Informed Consent

All subjects who are enrolled in the trial will be eligible to participate in the optional PGt analysis (except in countries where collection of PGt samples is not allowed). Participation is optional, and the subjects who choose to participate will need to sign a specific PGt ICF.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Confidentiality of Pharmacogenetic Data

The results of the genetic analysis are for research purposes only. The results of the genetic tests will not be made available to the subject, members of his/her family, his/her personal physician, or other third parties, except as specified below.

Unless otherwise required by law or by regulatory authorities for the purpose of verifying information obtained from this trial, only the Sponsor's authorized personnel and agents will have access to the confidential genetic data. The results of the PGt part of the trial may be submitted to the regulatory authorities and governmental agencies in countries where the IMP may be considered for approval; however, the subject will be identified by trial number and subject number only. The subject will not in any case be identifiable in reports or publications resulting from this trial.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, s/he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, Merck Serono/EMD Serono provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (the ICF, IB, subject questionnaires, and subject diaries) to the responsible IEC/IRB for its favorable opinion/approval.

The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at an external service provider (Trial Master File documents will be transferred to the Sponsor at the completion of the trial).

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

The main purpose of the CRF is to obtain those data required by the clinical trial protocol in a complete, accurate, legible and timely fashion. The data in the CRF should be consistent with the relevant source documents.

The data collected in the course of this trial must be documented in the CRFs and/or the Adverse Event Safety Report Form (Clinical Trials). It is the Investigator's responsibility to ensure the accuracy of the data entered in the CRFs.

Details regarding CRF handling and instructions concerning CRF completion are provided in the MOP.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name,
- Date of birth,
- Sex,
- Height,
- Weight,
- Medical history and concomitant diseases,
- Prior and concomitant therapies, including nonpharmacological therapies for OA and the use of assistive devices for ambulation (e.g., cane) (including changes during the trial),
- Trial identification (EMR700692_006),
- Date of subject's inclusion into the trial (i.e., date of giving informed consent),
- Subject number in the trial,
- Dates of the subject's visits to the site,
- Any medical examinations and clinical findings predefined in the clinical trial protocol,

- Subject diaries,
- All AEs observed in the subject,
- Date of subject's end of trial, and
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes X-rays, MRI scan images, ECG recordings, and laboratory value listings. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The site Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at

the site, including the Investigator Site File, the completed CRFs, the IMP(s), and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Reports

Clinical Trial Reports according to ICH Topic E3 will be written by the Sponsor in consultation with the Coordinating Investigator.

It is planned to perform the statistical analysis in two steps, as described in Section 8.5.1. A detailed Clinical Trial Report will be written based on the data collected up to the end of the DBPC treatment phase, and long-term follow-up data will be analyzed and reported separately from the DBPC treatment phase results.

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint that will include data from all trial sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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12 Appendices

Appendix A: American College of Rheumatology Criteria for the Classification and Reporting of Osteoarthritis of the Knee

For this trial, please use the following reference:

Altman R, Asch E, Bloch D, Bole G, Borenstein K, Brandt W, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis & Rheumatism* 1986;29(8): 1039-49.

Table 4 Summary of Criteria for Classification of Idiopathic Osteoarthritis of the Knee

Clinical and Laboratory	Clinical and Radiographic	Clinical†
Knee pain + at least 5 of 9: <ul style="list-style-type: none"> • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • ESR < 40 mm/hour • RF < 1:40 • SF OA 	Knee pain + at least 1 of 3: <ul style="list-style-type: none"> • Age > 50 years • Stiffness < 30 minutes • Crepitus • Osteophytes 	Knee pain + at least 3 of 6: <ul style="list-style-type: none"> • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony Tenderness • Bony enlargement • No palpable warmth
92% sensitive	91% sensitive	95% sensitive
75% specific	86% specific	69% specific

ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count < 2,000/mm³).

† Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

Appendix B: Safety Laboratory Parameters

The following laboratory parameters will be measured.

Hematology	<ul style="list-style-type: none"> • White blood cell (WBC) count • Lymphocytes (absolute count, %) • Monocytes (absolute count, %) • Neutrophils (absolute count, %) • Eosinophils (absolute count, %) • Basophils (absolute count, %) • Red blood cells • Hematocrit • Hemoglobin • Platelets
Coagulation (screening assessment only; to be done locally)	<ul style="list-style-type: none"> • Partial thromboplastin time (PTT) • International Normalized Ratio (INR)
Clinical biochemistry	<ul style="list-style-type: none"> • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • Total protein • Total bilirubin • Creatine kinase (CK) • Creatinine • Calcium • Phosphorus • Sodium • Potassium • Magnesium • Blood urea nitrogen (BUN) • Glucose (not fasting) • Chloride • Albumin • High-sensitivity C-reactive protein (hsCRP) • Erythrocyte sedimentation rate (ESR) • Interleukin-6 (IL-6)
Urinalysis	<ul style="list-style-type: none"> • Dipstick parameters: • pH • Specific gravity • Protein • Glucose • Ketones • Bilirubin • Blood • Urobilinogen • Leukocytes
Pregnancy tests (to be done locally)	<ul style="list-style-type: none"> • Serum during screening; urine at other time points.
Immunogenicity	<ul style="list-style-type: none"> • Presence of antibodies to sprifermin/FGF-18

Instructions for sample collection, handling, and shipping are provided in the MOP.

Appendix C: Subject Questionnaires: WOMAC, MOS SF-36, and ICOAP

Subjects will complete all of the following questionnaires themselves.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Questionnaire

Appropriate translations of the entire WOMAC™ version 3.1 questionnaire (11-box numerical scale version) by PPD and the corresponding User's Guide 3.1 will be used.

For administration of the questionnaire, instructions for the WOMAC 3.1 Index should be followed.

The WOMAC™ version 3.1 questionnaire and User's Guide will be provided separately.

Medical Outcomes Study Short Form-36 General Health Survey (MOS SF-36)

Appropriate translations of the MOS SF-36 version 2.0 and the corresponding User's Manual will be used.

The MOS SF-36 questionnaire version 2.0 and User's Manual will be provided separately.

Measure of Intermittent and Constant Osteoarthritis Pain Questionnaire (ICOAP)

Version 3 of the ICOAP questionnaire and the corresponding User's Guide will be used in this trial.

The ICOAP will only be used in countries for which an appropriate validated translation of the questionnaire is available.

For administration of the questionnaire, instructions in the User's Guide for the ICOAP, version 3, should be followed. In this trial, the questionnaire will be completed by the subject.

The questionnaire and the corresponding User's Guide will be provided separately.

Appendix D: Knee Injury and Osteoarthritis Outcome Score Quality of Life (KOOS QOL) and Symptom Index Subscales

The KOOS QOL consists of the following 4 questions, to be evaluated by the subject using the indicated 5-point scales.

Q1. How often are you aware of your knee problem?

Never

Monthly

Weekly

Daily

Constantly

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all

Mildly

Moderately

Severely

Totally

Q3. How much are you troubled with lack of confidence in your knee?

Not at all

Mildly

Moderately

Severely

Extremely

Q4. In general, how much difficulty do you have with your knee?

None

Mild

Moderate

Severe

Extreme

The KOOS Symptom Index consists of the following 5 questions, to be evaluated by the subject using the indicated 5-point scales with the following instructions:

These questions should be answered thinking of your knee symptoms during the **last week**:

Q1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Q5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix E: Schedule of Trial Procedures

Table 5 Schedule of Trial Procedures for Visits 1 to 11

Visit	Screening ⁽¹⁾		Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	
	V1a	V1b	V2										
Week ⁽²⁾	-42 to -4 days		0 ⁽³⁾	1	2	3	12	26	27	28	29	38	
Informed consents ⁽⁴⁾	X												
Demographics	X												
Medical/medication history	X												
Inclusion/Exclusion criteria	X	X	X										
Withdraw analgesia prior to visit ⁽⁵⁾		X	X				X	X				X	
Identification of target knee		X											
Randomization				X									
WOMAC (question 1 only)	X	X											
WOMAC (full questionnaire)			X				X	X				X	
Patient's Global Assessment	X		X				X	X				X	
KOOS QOL and Symptom Index			X				X	X				X	
PGIC							X	X				X	
Pain NRS both knees	X	X	X				X	X				X	
Pain in other joints			X					X					
MOS SF-36			X					X					
ICOAP			X				X	X				X	
AEs	Continuous												
Concomitant medications	Continuous												
Surgical procedures (target knee)	Continuous												
Review of subject diaries		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ⁽⁶⁾		X		X	X	X	X	X	X	X	X	X	X
Physical examination ⁽⁷⁾		X					X	X					
ECG		X											
Clinical laboratory specimens ⁽⁸⁾		X		X				X					
Antibodies to sprifermin/FGF-18				X		X		X			X		
PK serum collection ⁽⁹⁾				X		X					X		
Biomarker serum collection ⁽¹⁰⁾				X							X		
Biomarker urine collection				X							X		
PGt sample collection ⁽¹¹⁾	One sample needed. Can be obtained at any trial visit, preferably at baseline.												
Pregnancy test ⁽¹²⁾		X		X	X	X			X	X	X		
20-meter walk test		X	X					X	X			X	
Knee X-ray(s) ⁽¹³⁾⁽¹⁴⁾		X											
Target knee MRI ⁽³⁾⁽¹⁴⁾				X				X					
Synovial fluid collection ⁽¹⁵⁾				X	X	X		X	X	X			
i.a. injection of IMP				X	X	X		X	X	X			

Table footnotes appear on following page.

Abbreviations: AEs: adverse events; ECG: electrocardiogram; i.a: intra-articular; ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain; KOOS: Knee Injury and Osteoarthritis Outcome Score; MRI: magnetic resonance imaging; NRS: numerical rating scale; PGIC: Patient Global Impression of Change; PK: pharmacokinetic; QOL: quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Subjects will be requested to discontinue the intake of any pain medications for at least 5 half-lives before a visit involving completion of the WOMAC.

At visits where IMP is administered, all procedures should be performed before dosing unless otherwise specified. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS in both knees, pain in other joints, MOS SF-36, and ICOAP) should be completed before any other procedures are performed; the WOMAC should be completed first.

At each visit, subjects will be given trial diaries which will be collected and reviewed at the following visit (see Section 7.1.1).

1. After informed consent for the trial is obtained, screening procedures can be spread out over this period if necessary for logistical reasons. However, subject questionnaires (WOMAC question 1, PGA, and NRS pain) must be completed on the same day at the beginning of screening. Subjects not taking analgesic medication at the time of informed consent signature can have Visit 1a and 1b procedures completed at the same visit. If Visit 1a and 1b are being combined do not repeat the WOMAC Question 1 or the NRS pain score. See Section 7.1.2 for details.
2. Study visits, beginning with Visit 3, should be planned for the study day specified in the protocol. If it is not possible to complete the visit on the planned day, or if an emergency occurs, the protocol does allow for some exceptions as long as the minimum and maximum between injection and between treatment cycle restrictions are maintained. See Section 7.1.1 for details.
3. If it is not possible to schedule an MRI scan for the same day as the other baseline assessments for logistical reasons, the baseline MRI may be performed up to 3 days after confirmation of eligibility by baseline WOMAC. Randomization and IMP administration will then take place on the day of the baseline MRI (following the scan), and subsequent visits will be planned relative to the day of IMP administration. If baseline procedures are done on different days, those shown in the first column must be performed on the day of the WOMAC, and those shown in the second column must be performed on the day of the MRI (the scan must be performed before IMP injection). If an MRI scan can be scheduled on the same day as the confirmation of eligibility, all procedures listed for the baseline visit (in either column) must be performed on the same day.
4. Study informed consent and separate PGt consent.
5. All pain medications must be withheld for at least 5 half-lives before any visit with a WOMAC assessment beginning with Visit 1b.
6. Sitting systolic and diastolic blood pressure, heart rate, and body temperature.
7. Including height and weight at screening and weight at Week 26/Visit 7.
8. Hematology, biochemistry, urinalysis. See [Appendix B](#) for complete list. Coagulation tests will be performed locally at the screening assessment only.
9. Blood samples for PK will be taken pre-dose at Week 0/Visit 2, and thereafter 2 hours after the last dose of each cycle.
10. Fasting samples for biomarker analysis.
11. PGt samples will be collected for consenting subjects only.
12. Pregnancy testing: serum during screening; urine at subsequent time points (prior to IMP injection) and prior to each X-ray and MRI.
13. X-rays of both the target and the contralateral knee will be taken during screening, at Week 104/Visit 22/Early Termination, and at the last EFU visits; X-rays of only the target knee will be taken at other time points. During screening, a long-axis view of the target knee will be taken in addition to the anterior/posterior view.
14. At time points where IMP administration is scheduled, X-rays and MRIs may be performed up to 3 days before the planned day of IMP administration. At time points where there is no IMP administration scheduled, X-rays and MRIs may be performed within ± 4 days (DBPC treatment phase) or ± 7 days (extended follow-up phase) of the planned day.
15. At visits where IMP is injected, synovial fluid will be collected as part of the i.a. injection procedure, using the same needle that will be used for IMP injection. PK will be analyzed in synovial fluid at all indicated sampling time points. If the volume of synovial fluid collected permits, biomarkers will also be analyzed at Week 0/Visit 2 and at Week 26/Visit 7.

Table 6 Schedule of Trial Procedures for Visits 12 to 22 and Extended Follow-up Visits

Visit	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22/ ET	V23 (EF1)	V24 (EF2)	V25 (EF3)	V26 (EF4)	V27 (EF5)	V28 (EF6)	
Week⁽¹⁾	52	53	54	55	64	78	79	80	81	90	104	130	156	182	208	234	260	
Withdraw of analgesia prior to visit	X				X	X				X	X	X	X	X	X	X	X	
WOMAC	X				X	X				X	X	X	X	X	X	X	X	
PGA	X				X	X				X	X	X	X	X	X	X	X	
KOOS QOL and Symptom Index	X				X	X				X	X	X	X	X	X	X	X	
PGIC	X				X	X				X	X	X	X	X	X	X	X	
NRS in both knees	X				X	X				X	X	X	X	X	X	X	X	
Pain in other joints	X					X					X	X	X	X	X	X	X	
MOS SF-36	X					X					X	X	X	X	X	X	X	
ICOAP	X				X	X				X	X	X	X	X	X	X	X	
AEs	Continuous																	
Concomitant medications	Continuous																	
Surgical procedures (target knee)	Continuous																	
Review of subject diaries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ⁽²⁾	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination ⁽³⁾	X				X	X				X	X	X	X	X	X	X	X	
ECG	X										X							
Clinical laboratory specimens ⁽⁴⁾	X					X					X	X	X	X	X	X	X	
Antibodies to sprifermin/FGF-18	X			X		X			X		X							
PK serum collection ⁽⁵⁾			X					X			X							
Biomarker serum collection ⁽⁶⁾			X					X			X							
Biomarker urine collection			X					X			X							
PGt sample collection ⁽⁷⁾	One sample is needed. It can be taken at any trial visit.																	
Pregnancy test (urine) ⁽⁸⁾	X					X					X		X		X		X	
20-meter walk test	X				X	X				X	X	X	X	X	X	X	X	
Knee X-ray ⁽⁹⁾⁽¹⁰⁾	X										X		X		X		X	
Target Knee MRI ⁽¹⁰⁾	X					X					X		X		X		X	
Synovial fluid collection ⁽¹¹⁾	X	X	X			X	X	X										
i.a. injection of IMP	X	X	X			X	X	X										

Table footnotes appear on following page.



Abbreviations: AEs: adverse events; ECG: electrocardiogram; i.a: intra-articular; ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain; KOOS: Knee Injury and Osteoarthritis Outcome Score; MRI: magnetic resonance imaging; NRS: numerical rating scale; PGIC: Patient Global Impression of Change; PK: pharmacokinetic; QOL: quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
ET: Early Termination (procedures shown for this visit should be performed at the time of early treatment discontinuation or trial withdrawal.) EF: Extended follow-up.

Subjects will be requested to discontinue the intake of any pain medications for at least 5 half-lives before a visit involving completion of the WOMAC.

At visits where IMP is administered, all procedures should be performed before dosing unless otherwise specified. Subject questionnaires (WOMAC, PGA, KOOS QOL, KOOS Symptom Index, PGIC, NRS in both knees, pain in other joints, MOS SF-36, and ICOAP) should be completed before any other procedures are performed; the WOMAC should be completed first.

At each visit, subjects will be given trial diaries which will be collected and reviewed at the following visit (see Section 7.1.1).

1. Study visits, beginning with Visit 3, should be planned for the study day specified in the protocol. If it is not possible to complete the visit on the planned day, or if an emergency occurs, the protocol does allow for some exceptions as long as the minimum and maximum between injection and between treatment cycle restrictions are maintained. See Section 7.1.1 for details.
2. Sitting systolic and diastolic blood pressure, heart rate, and body temperature.
3. Including weight every six months (Weeks 78 and 104; Visits 17 and 22 in the treatment phase and all visits in the extended follow-up phase) and height at the end of the DBPC phase (Week 104/Visit 22/Early Termination) and last extended follow-up visit.
4. Hematology, biochemistry, urinalysis. See [Appendix B](#) for complete list. Coagulation tests will be performed locally at the screening assessment only.
5. Blood samples for PK will be taken 2 hours after the last dose of each cycle.
6. Fasting samples for biomarker analysis.
7. PGt samples will be collected for consenting subjects only.
8. Urine pregnancy test at scheduled time points (prior to IMP injection) and prior to each X-ray and MRI.
9. X-rays of both the target and the contralateral knee will be taken during screening, at Week 104/Visit 22, and at the last EF visits; X-rays of only the target knee will be taken at other time points. During screening, a long-axis view of the target knee will be taken in addition to the anterior/posterior view.
10. At time points where IMP administration is scheduled, X-rays and MRIs may be performed up to 3 days before the planned day of IMP administration. At time points where there is no IMP administration scheduled, X-rays and MRIs may be performed within ± 4 days (DBPC treatment phase) or ± 7 days (extended follow-up phase) of the planned day.
11. At visits where IMP is injected, synovial fluid will be collected as part of the i.a. injection procedure, using the same needle that will be used for IMP injection. PK will be analyzed in synovial fluid at all indicated sampling time points. If the volume of synovial fluid collected permits, biomarkers will also be analyzed at Week 52/Visit 12.

Appendix F: Pain in Other Joints

