Document title	**CLINICAL STUDY PROTOCOL**
Study official title	**Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis.** A 52-week international, multi-regional, multi-center, randomized, double-blind, placebo-controlled, dose-ranging study.
Study brief title	**Efficacy of S201086/GLPG1972 in patients with knee osteoarthritis**
Test drug code	**S201086/GLPG1972**
Indication	**Osteoarthritis**
Development phase	**Phase 2**
Protocol code	**CL2-201086-002/GLPG1972-CL-201**
EudraCT Number	**2017-004581-10**
Universal Trial Number	**U1111-1205-0321**
Investigational New Drug Application Number	**133039**
Sponsor	**GALAPAGOS NV (US)** **Institut de Recherches Internationales Servier (I.R.I.S.) (ex-US)**
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Version of the document	**Final version** **CONFIDENTIAL**

Galapagos NV, Industriepark Mechelen Noord, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium

Confidentiality statement

STUDY SUMMARY SHEET

Name of the sponsor: I.R.I.S. (ex-US)/Galapagos NV (US)	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
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Title of study:
Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis. A 52-week international, multi-regional, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study.
Protocol No.: CL2-201086-002/GLPG1972-CL-201

National Coordinators and Investigators
National coordinators and investigators: listed in a separate document.

Study centers:
Planned total number of centers=90-110
Planned total number of countries=12-15

Study period:	**Study development phase: 2**
- Study duration for the patient: max. 61 weeks - Study initiation date (FVFP): Q2 2018 - Study completion date (LVLP): Q4 2020	

Objectives:

The objectives of this study are to evaluate the efficacy and safety of 3 doses of S201086/GLPG1972 compared to placebo in patients with knee osteoarthritis (OA).

The primary objective of the study is to demonstrate the efficacy of at least one dose (among 3 doses) of S201086/GLPG1972 compared to placebo after 52 weeks of treatment in reducing cartilage loss measured by cartilage thickness using quantitative magnetic resonance imaging (qMRI) of the central medial tibiofemoral compartment (cMTFC) of the target knee.

The secondary objectives are:

To assess the safety and tolerability of 3 doses of S201086/GLPG1972.

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on:

- ✓ the proportion of "structural progressors*" based on cartilage thickness using qMRI of the cMTFC of the target knee
- ✓ pain, function, and stiffness measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
- ✓ pain measured with a 100-mm visual analog scale (VAS)
- ✓ patient global assessment (PGA) of disease activity measured with 100-mm VAS
- ✓ reduction of cartilage loss measured by cartilage thickness using qMRI of the total tibiofemoral compartment (tTFC) of the target knee
- ✓ Joint Space Width (JSW) measured by x-ray

**defined as patient who had at least 8% cartilage loss in the cMTFC between baseline and week 52 (W052).*

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 28 and 52 weeks of treatment on bone area using qMRI of the medial femoral condyle surface of the target knee.

To assess the pharmacokinetics of S201086/GLPG1972 (and metabolite[s] if applicable).

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on analgesic consumption.

Exploratory objectives are:

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To assess effect of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on:
- ✓ alanine-arginine-glycine-serine (ARGS) biomarker
- ✓ cartilage and bone degradation biomarkers

To assess influence of genes sequences or expression on patient's response to treatment

To evaluate a dose-response relationship between the 3 doses of S201086/GLPG1972.

To assess the relationship between exposure and pharmacodynamics (as safety and efficacy).

Methodology:
Study design: international, multi-regional, multicenter, randomized, double-blind, parallel groups, placebo-controlled dose-ranging phase 2 study.
The randomization will be stratified by region (Asia and Rest of the World).

The study will consist of:
- Screening period without study treatment: up to 5 weeks to assess the eligibility of patients
- Randomization and double-blind treatment period: 52 weeks with 4-parallel groups (doses: 75, 150 and 300 mg/day of S201086/GLPG1972 and matching placebo)
- Follow-up period without study treatment: 2 weeks

A Data and Safety Monitoring Board (**DSMB**) will be put in place in order to independently review the available safety data at regular pre-specified time points. The functioning of this DSMB is specified in a separate DSMB charter.

Number of patients:
Planned: 852 patients
Per treatment group (arm): 213 patients

Diagnosis and main criteria for inclusion:
The target population is male or female of non-childbearing potential patients suffering from mild to moderate clinical and radiologic knee OA.
Main screening criteria are:
Male patients or female patients of non-childbearing potential, age 40-75 years (both inclusive), body weight > 40 kg, body mass index (BMI) < 40 kg/m^2, diagnosed for knee osteoarthritis based on **clinical and radiological criteria** of the American College of Rheumatology, with a history of knee pain for at least 6 months and on the majority of days (> 50%) during the preceding month and with a severity ≥ 40 mm and ≤ 90 mm on VAS (100 mm). Patients will be selected based on symptom severity defined by a pain ≥40 mm and ≤90 mm on a 100 mm VAS at screening and inclusion visits, with knee OA classified as radiographic grade 2 or 3 of the Kellgren and Lawrence (KL) scale and OARSI grade 1 or 2 medial tibiofemoral joint space narrowing (JSN) and will have a documented need for symptomatic as needed-treatment for OA in the target knee with systemic non-steroidal anti-inflammatory drugs (NSAIDs) and/or other analgesics.

Investigational Medicinal Product (IMP): test drug and comparator:
Test drug:
Name: S201086/GLPG1972
Doses: 75 mg – 150 mg – 300 mg
Dosage form: film-coated tablet containing 75 mg S201086-1/G504572 (S201086-1/G504572 is the compound code for S201086/GLPG1972)

Comparator:
Name: placebo
Dosage form: film-coated matching tablet

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Mode of administration: take 4 tablets once a day, from the blister, with a glass of water, preferably in the morning

Duration of treatment:
Run-in period: no treatment up to 5 weeks of screening period
Active treatment period: fifty-two (52) weeks of treatment period
Follow-up period: no treatment during 2 weeks follow-up period

Criteria for evaluation:
Efficacy measurements:

Primary efficacy endpoint:
The change from baseline to W052 in cartilage thickness of the cMTFC of the target knee: qMRI.

Secondary efficacy endpoints:
- Proportion of structural progressors at W052 based on cartilage thickness of the cMTFC of the target knee: qMRI
- The change from baseline to W052 in WOMAC subscales scores of the target knee for pain, function and stiffness
- The change from baseline to W052 in pain of the target knee: 100-mm VAS
- The change from baseline to W052 in PGA of disease activity of the target knee: 100-mm VAS
- The proportion of Outcome Measures in Rheumatology (OMERACT)-OARSI responders** at W052: defined according to WOMAC and PGA
- The change from baseline to W052 in cartilage thickness of the tTFC of the target knee: qMRI
- The change from baseline to W028 and to W052 in bone area of the medial femoral condyle surface of the target knee: qMRI
- The change from baseline to W052 in JSW of the target knee: X-Ray
- Pain: Analgesic consumption at every visit up to W052

*** based on OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited Pham et al. 2004. Defined according to WOMAC and patient's global assessment as a patient who had:*
- *high improvement in pain or in function ≥ 50% and absolute change ≥ 20 or*
- *moderate improvement in at least 2 of the 3 following:*
  - *Pain ≥ 20% and absolute change ≥ 10*
  - *Function ≥ 20% and absolute change ≥ 10*
  - *Patient's global assessment ≥ 20% and absolute change ≥ 10.*

Other secondary endpoints:

Safety:

The safety and tolerability assessed by the incidence of adverse events (AEs), changes over time in safety parameters and incidence of abnormal safety parameters throughout the study.

Pharmacokinetics:

Pharmacokinetics of S201086/GLPG1972 (and metabolite[s] if applicable)
Exploratory endpoints:
- Biomarker of drug activity:
  - The change from baseline to each post baseline (W004, W012, W028, and W052) visits in ARGS concentration (serum)

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- The value at baseline and at each post baseline (W004, W012, W028, and W052) visits in ARGS concentration (serum)

- Biomarkers of cartilage (uCTX-II) and bone (sCTX-I, uCTXIα) degradation (serum and/or plasma and/or urine):
  - The change from baseline to each post baseline (W004, W012, W028, and W052) visits.
  - The value at baseline and at each post baseline (W004, W012, W028, and W052) visits.

  This list of biomarkers could be updated according to markers that may appear in the literature in the coming years

Optional genomic analysis of DNA/RNA.

Statistical methods:

Analysis sets:

- **Randomized Set (RS):**
  All patients to whom a therapeutic unit was randomly assigned using interactive web response system IWRS.
- **Safety Set (SS):**
  All patients having taken at least one dose of IMP.

Sample size calculation:

The determination of the sample size was performed considering the change from baseline to W052 in cartilage thickness in the cMTFC, expressed in mm and measured by qMRI.

The primary objective is to demonstrate that at least one S201086/GLPG1972 dose is superior to placebo in the RS, based on a two-sided Dunnett test for multiple comparisons. The Dunnett test is used in order to maintain the experiment wise type I error at 5% (two-sided setting).

Two hundred and thirteen (213) patients per treatment group will provide a minimal power of approximately 70% to conclude for at least one dose that S201086/GLPG1972 is superior to placebo if the true difference is 0.0825mm for at least one dose, assuming a standard deviation of 0.30mm (Lohmander et al., 2014).

Efficacy analysis:

In order to take into account the multiplicity of comparisons induced by the assessment of three S201086/GLPG1972 doses versus placebo, a Dunnett procedure will be used.

Primary endpoint:

In order to meet the primary objective of the study, the efficacy of at least one dose of S201086/GLPG1972 as compared to placebo after 52 weeks of treatment in reducing cartilage loss in patients with knee OA will be assessed from the change from baseline to W052 in cartilage thickness as measured in the medial central tibiofemoral compartment on the target knee, in patients of the RS. A restricted maximum likelihood (REML)-based, mixed-effects model for repeated measures approach (so called Mixed-effects Model for Repeated Measures – MMRM) using all longitudinal observations at each post-baseline visit will be used (main analysis). The MMRM as a primary analysis will assume that patients would keep the benefit of the randomized treatment after study discontinuation. For patients with an early discontinuation from the study (delay between the Early Termination and baseline less than 2 months) and without any post baseline measurement of cartilage thickness, a multiple imputation procedure will be used to impute the missing evaluations. The treatment comparisons associated with the primary analysis will be the contrasts between each dose of S201086/GLPG1972 and placebo at the change from baseline to W52. Analysis will include the fixed, categorical effects of treatment, regions,

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time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline, time-by-baseline interaction.

The analysis will fit an unstructured covariance matrix, and the assumptions underlying the model will be checked.

The consistency of the results between the Asian population and the non-Asian population will be evaluated on primary endpoint, according to the Method 2 defined in Ministry of Health Labor and Welfare Notification (MHLW) Notification "Basic principles on Global Clinical Trials". Treatment effect estimates and confidence intervals will be provided, for each dose, in Asian population and non-Asian population. In case of a statistically significant overall treatment effect (in favor of S201086/GLPG1972) at a considered dose, the results will be considered consistent if the observed treatment effects in Asian and non-Asian patients are in favor of S201086/GLPG1972.

Sensitivity analyses will be performed to assess the robustness of the primary analysis results to the method of handling missing data.

Secondary endpoints:

For the proportion of "structural progressors" and proportion of OMERACT-OARSI responders at W052, the difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS, considering a multiple imputation for handling all missing data and using a logistic model, including the fixed, categorical effects of treatment, regions (Asia and Rest of the World), as well as the continuous, fixed covariates of baseline.

The difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS, on continuous secondary efficacy endpoints at W052, with the same strategy as the main analysis of the primary endpoint: multiple imputation for patients without any post-baseline value followed by a MMRM using all the longitudinal observations at each post-baseline visit. Analysis will include the fixed, categorical effects of treatment, regions (Asia Rest of the World), visit and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline, visit-by-baseline interaction.

For the change from baseline to W052 in JSW and the change from baseline to W028 in bone area, the difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS at W052 (respectively W028), considering a multiple imputation method for handling all missing data at W052 (respectively W028), and using an ANCOVA. Analysis will include the fixed, categorical effects of treatment, regions (Asia, US and Rest of the World), as well as the continuous, fixed covariate of baseline.

For analgesic consumption, number and percentage of patients by treatment reported will be provided, overall and by treatment group.

For each treatment group, descriptive statistics will be provided for all secondary endpoints, overall and by regions.

Study patients (disposition, baseline characteristics and follow-up) and safety analysis:
Descriptive statistics will be provided.

Pharmacokinetic analysis:
Plasma concentrations of S201086/GLPG1972 (and those of metabolite[s] if applicable) will be documented with descriptive statistics (mean, median, standard deviation, minimum and maximum) at each time-point and each dose for trough plasma concentration (Ctrough) values.

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S201086/GLPG1972 (and metabolite[s] if applicable) plasma concentration measurement will be used in order to build a population pharmacokinetics model. This analysis will provide pharmacokinetic parameters and their associated variability. The influence of covariates will be investigated. The pharmacokinetic analysis will be described in separate Data Analysis Plan (DAP) and report.
Exploratory assessment of the relationship between exposure and pharmacodynamics (as safety and efficacy) will be performed and if applicable, population pharmacokinetic-pharmacodynamic models will be developed and a DAP will be set up and reported separately.

Contractual signatories

I, the undersigned, have read the foregoing protocol and the "Patient information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice (GCP) and the applicable regulatory requirements.

NAME DATE SIGNATURE

INVESTIGATOR :

CENTER NUMBER	

GALAPAGOS NV REPRESENTATIVE

CLINICAL DEVELOPMENT LEADER: **HENRI DECKX** 02-MARCH-2018

EMERGENCY CONTACT INFORMATION – US ONLY

In case of medical **questions** during the course of the study, the investigator must contact the CRO Medical Monitor or, if unavailable, his/her back up.

CRO Medical Monitor:
Alicia Weeks, MD
Phone number: (+1) 513.579.9911 (ext. 12986)
Mobile: (+1) 513-673-5860
Email: A.Weeks@Medpace.com

Back up:
Terence Eagleton, MBBS
Phone number: (+44) 208.563.5900 (ext. 25777)
Mobile: (+44) 778.950.4390
Email: T.Eagleton@Medpace.com

Sponsor Back-up contact:

+32 52 26 23 59

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List of abbreviations

AE	:	adverse event
ACR	:	American College of Rheumatology
ADAMTS	:	a disintegrin and metalloproteinase with thrombospondin motif
ADL	:	activities of daily living
ALT	:	ALanine aminoTransferase
ALP	:	alkaline phosphatase
Alu	:	aluminum
ANCOVA	:	analysis of covariance
ARGS	:	alanine-arginine-glycine-serine
AST	:	ASpartate aminoTransferase
AUC_{0-24h}	:	area under the plasma concentration-time curve from time 0 t 24 hours postdose
$AUC_{0-\infty}$	:	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{τ}		area under the concentration-time curve for the dosing interval
BAP	:	blood arterial pressure
BINAP	:	(+/-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMI	:	Body Mass Index
bpm	:	beats per minute (heart rate unit)
C_{max}	:	maximum observed plasma concentration
CMP	:	clinical monitoring plan
cMTFC	:	central medial tibiofemoral compartment
CPK	:	creatinine phosphokinase
CRO	:	Contract Research Organisation
CRP	:	C-reactive protein
CTX-I	:	C-terminal Telopeptide of type I Collagen
CTX-II	:	C-terminal Telopeptide of type II Collagen
CSP	:	Clinical Study Protocol
CTCAE	:	Common Terminology Criteria for Adverse Events
C_{trough}	:	trough plasma concentration
CV	:	curriculum vitae
CYP	:	cytochrome P450
DAP	:	data analysis plan
DBP	:	diastolic blood pressure
DC	:	direct compression
DMM	:	destabilization of the medial meniscus
DMOAD	:	disease modifying osteoarthritis drug
DSMB	:	data safety monitoring board
EAE	:	emergent adverse event
$Eavg_{(0-24h)}$	:	average % reduction from time 0 to 24 h postdose
ECG	:	electrocardiogram
eCRF	:	electronic case report form
e.g.	:	*exempli gratia* (for example)
EMA	:	European Medicines Agency
ePRO	:	electronic patient reported outcome
ERIN	:	Event Requiring Immediate Notification

g	:	gram
GAG	:	glycosaminoglycan
GCP	:	Good Clinical Practice
GFR	:	glomerular filtration rate
GGT	:	gamma glutamyl transferase (Gamma-Glutamyl Transpeptidase)
GLP	:	Good Laboratory Practice
h	:	hour
HBs	:	Surface antigen of Hepatitis B virus
HCV		hepatitis C virus
HDL	:	high density lipoprotein
hERG	:	human ether-a-go-go related gene
HIPAA	:	Health Insurance Portability and Accountability Act
HIV	:	human immunodeficiency virus
HR	:	heart rate
IC_{50}	:	half maximal inhibitory concentration
ICF	:	informed consent form
ICH	:	International Conference on Harmonisation
i.e.	:	*id est* (that is)
IEC	:	independent ethics committee
IL1α	:	interleukin-1 alpha
IL1β	:	interleukin-1 beta
IMP	:	Investigational Medicinal Product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial (test drug / placebo)
IND	:	Investigational New Drug
INR	:	international normalized ratio
IRB	:	institutional review board
I.R.I.S.	:	Institut de Recherches Internationales Servier
IU	:	International Unit
IWRS	:	interactive web response system
JSN	:	joint space narrowing
JSW	:	joint space width
kg	:	kilogram
KL	:	Kellgren and Lawrence system for classification of knee osteoarthritis (X-ray)
L	:	liter
LDH	:	lactate dehydrogenase
LDL	:	low density lipoprotein
MCH	:	mean corpuscular hemoglobin
MCHC	:	mean corpuscular hemoglobin concentration
MCV	:	mean corpuscular volume
MDRD	:	Modification of the Diet in Renal Disease
MedDRA	:	Medical Dictionary for Regulatory Activities
mg	:	milligram
min	:	minute
MHLW	:	Ministry of Health Labor and Welfare Notification
mL	:	Milliliter
mm	:	Millimeter
mmHG	:	Millimetre of mercury

mmol	:	millimole
MMP	:	matrix metalloproteinase
MMRM	:	mixed-effects model for repeated measures
MNX	:	meniscectomy
MRI	:	magnetic resonance imaging
MTFC	:	Medial Tibiofemoral Compartment
msec	:	millisecond
µmol	:	micromole
NDA	:	New Drug Application
ng	:	nanogram
NOAEL	:	no observed adverse effect level
NSAIDS	:	non-steroidal anti-inflammatory drugs
NYHA	:	New York Heart Association
OA	:	osteoarthritis
OARSI	:	Osteoarthritis Research Society International
OMERACT	:	Outcome Measures in Rheumatology
PCSA	:	Potentially Clinically Significant Abnormalities
PGA	:	patient global assessment
PVC	:	polyvinylchloride
QC	:	quality control
q.d.	:	*quaque die*, once daily
qMRI	:	quantitative magnetic resonance imaging
QTcF	:	QT interval corrected for heart rate by Fridericia formula
REML	:	restricted maximum likelihood
RR	:	respiratory rate
RS	:	Randomized Set
SAE	:	serious adverse event
SAP	:	statistical analysis plan
SAR	:	Serious Adverse Reactions
SBP	:	Systolic Blood Pressure
SCW	:	streptococcal cell wall
sec	:	second
SS	:	Safety Set
TEAE	:	treatment-emergent adverse event
$t_{½}$	:	terminal elimination half-life
tTFC	:	total tibiofemoral compartment
t.i.d.	:	ter in die (three times a day)
T/L	:	Tera (10^{12}) per litre
test drug	:	Drug substance in a given dosage form, tested in a clinical trial. It corresponds to S201086/GLPG1972 product
t_{max}	:	time to maximum observed plasma concentration
TSH	:	thyroid-stimulating hormone
TU	:	therapeutic unit
TUTF	:	Therapeutic Unit Tracking Form
ULN	:	upper limit of normal
V	:	Visit
VAS	:	visual analog scale
vs.	:	*versus*
W	:	week

WD	:	withdrawal
WG	:	wet granulation
WHO-DRUG	:	World Health Organization, Drug Dictionary
WMA	:	World Medical Association
WOCBP	:	women of child-bearing potential
WOMAC	:	Western Ontario and McMaster Universities Osteoarthritis Index

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Galapagos will act as sponsor of the Study in the United States of America (including its territories and possessions) (the "US Territory") and Servier will act as sponsor of the Study in all countries except the US Territory (the "ROW Territories"). Each of Galapagos and Servier shall be solely responsible for the activities conducted in their respective territories, *i.e.*, Galapagos for the US Territory and Servier for the ROW Territories.

Non-sponsor parties, sponsors parties, and contract research organization (CRO) parties responsible for local management of the study are described in a separate document.

The list of investigators for each country is given in separate documents attached to the protocol.

The composition and role of the supervisory committees are described in Sections 8.3 and 12.4.

2. BACKGROUND INFORMATION

S201086 is also developed by Galapagos N.V. under the code GLPG1972.

Definition and epidemiology of osteoarthritis
Osteoarthritis (OA) is a degenerative joint disease involving the structure of all joint tissues including articular cartilage, subchondral bone, ligaments, capsule, and synovial membrane. It may develop in any joint but most commonly affects the knees, hips, and hands.

The global prevalence of radiographically confirmed symptomatic OA has been estimated to be 3.8% for knee and 0.8% for hip (Cross, 2014), but this prevalence increases up to 10- 40% in the elderly ((WHO, 2013), Framingham OA study). The prevalence of OA is expected to increase in the upcoming years, mainly due to the increasing prevalence of obesity and the ageing population ((Elders, 2000); (Zhang W et al., 2010)).

Standard of care treatment
Standard of care is a combination of non-pharmacological and symptomatic pharmacological treatments which should be personalized to the need of the individual patient. Despite a number of investigations of potential therapies, there are currently no approved disease-modifying drugs. Effective and safe long-term treatment for most OA patients is thus not available, creating a clear unmet medical need for structural protection (Karsdal, 2016).

Aggrecanase in OA
Degradation of the cartilage extracellular matrix is a central feature of OA and is widely thought to be mediated by proteinases that degrade structural components of the matrix, primarily aggrecan and collagen. Among the different attempts to develop new agents for OA, inhibition of aggrecanase activity in diseased cartilage is thus considered a valid therapeutic approach (Karsdal, 2016). Aggrecan plays a central role on cartilage compressibility and elasticity during exercises or movements.

In OA, aggrecan is proteolyzed mainly by matrix metalloproteases (MMPs) and aggrecanases (a disintegrin and metalloproteinase with thrombospondin motifs [ADAMTS] 4 and -5). The cleavage of aggrecan by ADAMTS-5 is a crucial event in OA pathogenesis, both in rodents and in humans ((Fosang, 2008); (Verma and Dalal, 2011)). By breaking down the interaction between aggrecan and important structural components of the extracellular matrix (Heinegard and Saxne , 2011), an early event in OA, it favors the degradation of the matricial network of cartilage and alters the pericellular environment, ultimately leading to chondrocyte death.

The important contribution of ADAMTS-5 to OA pathogenesis was first demonstrated in preclinical models of OA. In a model of OA induced by destabilization of the medial meniscus, ADAMTS-5 knockout mice were protected from cartilage degradation (Glasson et al., 2005). Additionally, early preclinical candidates (small chemical entities/antibodies) demonstrated chondroprotective activity linked to ADAMTS-5 inhibition in animal models of OA ((Chockalingam, 2011); (Chiusaroli, 2013); (Chen P et al., 2014), (Caselli et al., 2015)). Importantly, ADAMTS-5 deficient mice did not develop mechanical allodynia associated with osteoarthritis, demonstrating that in addition to disease modifying OA drug (DMOAD) activity, ADAMTS-5 inhibition was also effective in pain relief in this model (Malfait et al., 2010); (Miller et al., 2016).

Degradation of aggrecan by ADAMTS-5 was identified as being involved in patients with OA. The expression of ADAMTS-5 was increased in articular cartilage samples obtained from OA patients (Chen S et al., 2014), and several studies reported that aggrecan fragments (ARGS, NITEGE) generated after cleavage at the aggrecanase site were found at higher levels in cartilage, synovial fluid and sera from OA patients (Lohmander et al., 1993); (Sandy and Verscharen, 2001); (Struglics et al., 2011); (Zhang E et al., 2013); (Germaschewski, 2014). It was also demonstrated that compared to MMPs, ADAMTS-5 was the major contributor to aggrecan catabolism during OA (Lohmander et al., 1993); (Sandy, 2006); (Durigova, 2011).

Aggrecan cleavage by ADAMST-5 results in the release of the N-terminal neo-epitope ARGS fragments and these fragments were found to be increased in human knee synovial fluid and blood after joint injuries in OA patients waiting for a total knee replacement (Larsson et al., 2014).

In conclusion, ADAMTS-5 activity is exacerbated during OA, and its inhibition protects from cartilage degradation and is effective in reducing allodynia in preclinical models of OA, suggesting that it is a highly relevant target for DMOAD treatment.

Overview of S201086 / GLPG1972

S 201086 also named GLPG1972, is a potent and selective inhibitor of ADAMTS-5 currently being developed as an oral treatment for OA.

ADAMTS-5 (aggrecanase-2, ADAMTS-11) is a member of the ADAMTS protein family. ADAMTS-5 is expressed in many tissues, with highest expression in uterus, placenta, and cartilage. ADAMTS-5 is the major aggrecanase in experimentally induced OA mouse models. Aggrecan cleavage by ADAMTS-5 results in the release of the N-terminal ARGS neoepitope fragments and these fragments were found to be increased in human knee synovial fluid after joint injuries and in OA. The discovery that ADAMTS-5 plays a major role in OA suggests that this enzyme may be a suitable target for the development of new drugs designed to inhibit cartilage destruction in arthritis.

Nonclinical pharmacology data

S201086/GLPG1972 is a potent inhibitor of human ADAMTS-5 (hADAMTS-5) (half maximal inhibitory concentration [IC_{50}] = 20 nM) showing 8- and 7-fold selectivity over hADAMTS-4 and -6, respectively. This compound displayed high selectivity over a panel of selected MMPs and other ADAMTSs. The high selectivity of S201086/GLPG1972 was confirmed in the Cerep safety panel where, at 30 µM concentration, out of the 114 targets (receptors, channels, transporters, and enzymes) only the 5-HT_{2B} receptor was inhibited more than 50%.

S201086/GLPG1972 is a potent and specific inhibitor of aggrecanase-derived aggrecan degradation as shown in cartilage explants. In the mouse cartilage explant model, S201086/GLPG1972 was able to inhibit dose-dependently the glycosaminoglycan (GAG) release induced by interleukin-1 alpha (IL1α). In human cartilage explants, GLPG1972 dose-dependently inhibited production of aggrecanase-derived aggrecan fragments (“AGNx1” neoepitope assay) induced by interleukin-1 beta (IL1β).

S201086/GLPG1972 showed a dose-dependent chondroprotective effect in an acute *in vivo* model of cartilage depletion: at Day 4 in the streptococcal cell wall (SCW)-induced arthritis

mouse model, S201086/GLPG1972 was able to significantly protect against cartilage PG depletion. Most importantly S201086/GLPG1972 testing in the meniscectomized (MNX) rat model resulted in significant disease-modifying osteoarthritis drug (DMOAD) activity as measured by a reduction in the OARSI (Osteoarthritis Research Society International) score and a significant impact on a variety of histomorphometric parameters. The DMOAD activity of S201086/GLPG1972 was confirmed in a well-recognized murine model of OA, *i.e.*, the "destabilization of the medial meniscus (DMM) mouse model", where significant protection was observed against cartilage degradation and subchondral bone remodeling, two hallmarks of OA.

Safety pharmacology

The *in vitro* human ether-a-go-go related gene (hERG) assay with S201086/GLPG1972 did not raise any concerns. An *in vivo* study in telemetered monkeys did not show a relevant impact on cardiovascular parameters up to the dose of 400 mg/kg/day for 8 consecutive days. In a second *in vivo* study in telemetered dogs, GLPG1972 had no impact on cardiovascular parameters at the single dose of 20 mg/kg; at 60 and 120 mg/kg, increased heart rate (HR) values were observed, without a dose-response relationship and with a time-course not correlated with plasma concentrations of GLPG1972. No changes in blood arterial pressure (BAP) and electrocardiogram (ECG) parameters were observed in dogs.

GLPG1972 did not cause any biologically significant effects in respiratory and central nervous system parameters in rats up to 1000 and 300 mg/kg, respectively.

Toxicology

All the toxicological studies supporting the phase 2 clinical program have been performed.

S201086/GLPG1972 showed no genotoxic effects *in vitro*, in the Ames test and in the micronucleus assay in human lymphocytes, or *in vivo* in the peripheral blood micronucleus test in rats, up to the dose of 1000 mg/kg/day for 4 weeks.

Ames tests were also performed for (+/-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and G1171054, two impurities of the manufacturing process of GLPG1972, and the results showed no genotoxic potential.

Regarding repeat dose toxicity studies, S201086/GLPG1972 was administered by oral dosing for up to 26 weeks in rats and up to 39 weeks in dogs.

In the 26-week toxicity study in rats at doses of 70, 200, and 600 mg/kg/day by oral route, there were 2 unexplained deaths at the dose of 600 mg/kg/day. At the end of treatment period, nasal and lung findings were observed in rats at 200 and 600 mg/kg/day that were considered due to reflux associated with oral gavage dosing rather than with the test item. Both of these unscheduled deaths in the high dose group also showed the most severe signs of reflux-associated changes in their nasal cavities. As a consequence, these mortalities are considered most likely related to reflux as there appeared to be no alternative plausible explanation for the unscheduled deaths.

Due to the 2 unexplained mortalities, the no observed adverse effect level (NOAEL) was still considered to be 200 mg/kg/day for both males and females, with a mean sex combined area

under the plasma concentration-time curve from time 0 to 24 hours (h) postdose (AUC_{0-24h}) and maximum plasma concentration (C_{max}) of 79.9 µg.h/mL and 19.8 µg/mL, respectively, in Week 26.

In a 39-week GLP toxicity study in dogs at doses of 12.5, 25, 50, and 100/75 mg/kg/day by oral route, a decline in general condition and body weight loss was observed in the high dose group, triggering the decision to decrease the dose to 75 mg/kg/day from Week 26 onwards. The NOAEL was considered to be 50 mg/kg/day for both males and females with a mean sex combined C_{max} and AUC_{0-24h} of 51.1 µg/mL and 356 µg.h/mL, respectively, in Week 39.

In a segment I fertility study in rats at doses of 100, 300, and 1000 mg/kg/day by oral route, S201086/GLPG1972 was devoid of any effect on fertility in male rats. In females an adverse decrease in mean number of corpora lutea and increased percentage of pre- and post-implantation loss, leading to decreased litter sizes, was observed at the high dose of 1000 mg/kg/day. Based on these results, the NOAEL for male fertility and reproductive performance based on early embryonic development in the corresponding mated untreated females was set at 1000 mg/kg/day. The NOAEL for female fertility and subsequent early embryonic development was set at 300 mg/kg/day.

Clinical studies

Safety data

In Study GLPG1972-CL-101, administration of single (up to 2100 mg) and multiple (up to 1050 mg *q.d.* for 14 days) ascending oral doses of S201086/GLPG1972 in healthy subjects was well tolerated. No deaths, other serious adverse events (SAEs), or treatment-emergent adverse events (TEAE) leading to study drug discontinuation were reported during the study. All reported TEAEs were rated mild in intensity, were not dose-related, and were resolved by the end of the study.

In Study GLPG1972-CL-103, administration of single doses (600 mg) of S201086/GLPG1972 as oral solution in fasted state and as oral direct compression (DC) tablet in fasted and fed state in healthy male subjects was well tolerated. No deaths, other SAEs, or TEAEs leading to study drug discontinuation were reported during the study. All but 1 TEAE (moderate presyncope) were mild in intensity and all TEAEs were resolved by the end of the study.

In Study GLPG1972-CL-105, administration of a single dose (300 mg) of S201086/GLPG1972 as oral solution or wet granulation (WG) tablet in fasted state and as WG or DC tablet in fed state in healthy male subjects was well tolerated. No deaths or other SAEs were reported during the study. One subject experienced a TEAE of moderate migraine which led to study drug discontinuation. All other TEAEs were mild in intensity and all TEAEs were resolved/resolving by the end of the study.

In Study GLPG1972-CL-106, administration of 300 mg 201086/ GLPG1972 once daily (*q.d.)* for 10 days with or without a single 2-mg dose of midazolam in healthy male subjects was well tolerated. No deaths, other SAEs, or TEAEs leading to study drug discontinuation were reported during the study. All TEAEs were mild in intensity and all TEAEs were resolved by follow-up.

In Study GLPG1972-CL-104, administration of multiple oral doses of S201086/GLPG1972 (100, 200 or 300 mg *q.d.*) for 29 days in patients with OA was generally well tolerated. One

patient dosed with GLPG1972 300 mg *q.d.* prematurely discontinued the study due to an increase in alanine aminotransferase (ALT) on Day 15 ≥3 x the upper limit of normal (ULN), which was considered probably related to the study drug.

There were no overall trends in lab abnormalities over time or significant changes in vital signs, physical examinations, 12-lead ECG, and Holter parameters.

Overall, at the time of writing this protocol, the number of subjects/patients randomized in the clinical program was 113, of whom 101 to have been exposed to S201086/GLPG1972. The studies conducted enrolled 83 healthy adult male subjects aged 18-50 years and 30 (male and female) adult OA patients aged 50-75 years.

In general, the treatment was well tolerated. Up to now, no Serious Adverse Reactions (SARs), overdose, interaction, medication errors, abuse/misuse, pregnancy and/or lactation cases were reported and no life-threatening events or deaths occurred. No SAEs related to special patient groups were reported.

No specific important risks have been identified for S201086/GLPG at present. As with any new compound in early clinical development, cardiovascular safety, hepatic safety, biochemistry, hematology, coagulation and other laboratory safety parameters will be closely monitored throughout the clinical studies.

As there is limited clinical experience with S201086 so far, the study drug should not be administered to subjects with renal or hepatic impairment.

Pharmacokinetics

S201086/GLPG1972 given as a single dose oral solution, from 60 to 2100 mg, in the fasted state was rapidly absorbed with a median time to maximum concentration range of 1-4 h and eliminated with an overall mean apparent half-life of 10 h in healthy subjects.

After *q.d*. dosing for 14 days in healthy subjects, GLPG1972 exposure (both Cmax and area under the concentration-time curve for the dosing interval [AUC$_{\tau}$]) increased dose-proportionally over the entire dose range (300 to 1050 mg *q.d.*). Steady-state in S201086/GLPG1972 plasma concentrations was reached after 2 dosing days with a minimal accumulation. The excretion of unchanged 201086/GLPG1972 in urine over a 24 h period was less than 11% of the administered dose.

The PK parameters of S201086/GLPG1972 in patients with OA were not different from those observed in healthy subjects at the same dose level.

No food effect with the WG tablets of S201086/GLPG1972 (1.3- and 1.1-fold increase in C_{max} and area under the concentration-time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$], respectively) was observed.

After 10 daily doses of S201086/GLPG1972 in healthy subjects, co-administration with midazolam, a sensitive cytochrome P450 type 3A4 (CYP3A4) substrate, led to a slight decrease in midazolam exposure when compared to midazolam alone. The apparent midazolam terminal half-life was slightly reduced. As a result, S201086/GLPG1972 is classified as a weak inducer of CYP3A4 (decrease in substrate exposure between 20 and 50%).

Clinical pharmacodynamics

After a single administration of 300, 600, or 1050 mg of S201086/GLPG1972 in healthy subjects, no significant reduction of neoepitope ARGS levels *vs.* baseline was observed compared to placebo.

After dosing of 300, 600, or 1050 mg for 14 days, a significant reduction of ARGS levels *vs.* baseline was observed at Day 14 when compared to placebo. The mean average % reduction from time 0 to 24 h postdose ($Eavg_{(0\text{-}24h)}$) increased with the dose, but there were no statistically significant differences between the 3 tested doses. More subjects achieved a % reduction *vs.* baseline of at least 60% when receiving a higher dose of S201086/GLPG197. However there was no statistically significant dose-effect. Neoepitope ARGS were also determined in predose samples at Days 1, 3, 4, 5, 6, 8, 10, and 14. A progressive reduction over time was observed reaching a maximum inhibition of 50-60% at Day 14.

After dosing of 100, 200 or 300 mg for 29 days in patients with OA, a statistically significantly higher reduction compared with placebo in neoepitope ARGS levels vs. baseline was observed. The values of mean % reduction vs. baseline were dose-dependent. Neoepitope ARGS levels went back to baseline 14 and 21 days post-last dose (Day 43 and 50), indicating that the target engagement is reversible.

ARGS and other cartilage/bone biomarkers will be measured in phase 2 study in order to evaluate changes related to the treatment and/or the disease.

Rationale for study design

Recent literature provides strong evidence for a central role of ADAMTS-5 in OA and positions this enzyme as a key target for the discovery of DMOADs. GLPG1972 is a potent inhibitor of ADAMTS-5 which is capable to reach the joint cartilage upon oral administration and shows significant disease modification in 2 rodent surgery-induced OA models.

By virtue of these properties, it is expected that S201086/GLPG1972 would exert a particular benefit in patients with OA.

Study Design

The study is a prospective, international, multiregional, multicenter, randomized ratio: 1:1:1:1, double-blind, placebo-controlled, dose-ranging study. The objectives of this study are to evaluate the efficacy and safety of 3 doses of S201086/GLPG1972 compared to placebo in patients with knee OA and the primary objective is to demonstrate the efficacy of at least one dose (among 3 doses) compared to placebo in reducing cartilage loss of the target knee in these patients.

The 52-week treatment duration was chosen in order to observe minimum natural cartilage degradation in the placebo arm and ensure a sufficiently long exposure to treatment allowing the demonstration of the activity of the drug, and to collect relevant safety data on S201086/GLPG1972.

Study population

It is planned to randomize 852 patients (213 in each treatment arm). The target population will consist of patients diagnosed with knee OA based on the clinical and radiological criteria of the American College of Rheumatology (ACR) and classified as radiographic grade 2 or 3 of the Kellgren and Lawrence (KL) scale and grade 1 or 2 OARSI medial tibiofemoral joint space narrowing (JSN) (Altman et al., 2007). This population is likely to progress sufficiently to permit detection of cartilage loss as measured by cartilage thickness by quantitative magnetic resonance imaging (qMRI) (Lohmander et al., 2014); (Maschek, 2014)). This population is consistent with the recommendation of the current European Medicines Agency (EMA) guideline on clinical investigation of medicinal products used in the treatment of OA (CPMP/EWP/784/97 Rev.1, 2010) as well as OARSI recommendations for potential structure modifying drugs.

Study primary outcome

X-ray provides an indirect measure of the cartilage thickness, however only calcified bone can be visualized. Measurement of joint space width (JSW) has some evidence for construct and predictive validity, with good reliability and responsiveness; however studies of at least 1 and probably 2 years duration will be required. The choice to use qMRI for the primary outcome was based on the fact that this technique provides objective quantitative assessment of morphology (thickness, volume, and area) and integrity (quality) of the articular cartilage (Conaghan, 2011). (Eckstein et al., 2015) showed an association between loss in medial tibio-femoral cartilage thickness on qMRI and radiographic and pain progression in OA. It is expected that qMRI of cartilage thickness of the central medial tibiofemoral compartment (cMTFC) will have the highest responsiveness, allowing for observing significant changes after one year of treatment.

Choice of doses

The choice of doses (75, 150, and 300 mg daily) was based on pharmacokinetics and pharmacodynamics results in humans as well as data obtained in toxicological studies and pharmacological studies. Based on the conclusions of the Good Laboratory Practice (GLP) long-term chronic toxicity studies in rats and dogs, and the exposure at the highest dose to be administered in clinical studies (300 mg), safety margins of at least 1.2-fold for AUC *vs.* the most sensitive animal species (rat) are achieved. In dogs, a safety margin of 5 was calculated. In rats, this low safety margin is based on the occurrence of 2 treatment-related mortalities at the high dose level (600 mg/kg/day). These deaths are however most likely a result of reflux-related causes. In this context, safety margins for the maximum clinical dose of 300 mg/day compared to the 600 mg/kg/day rat dose would be about 2-fold. Moreover, the dose of 300 mg was well tolerated in healthy subjects and up to 1 months of treatment in patients with OA (GLPG1972-CL-104). The lower dose of 75 mg/day is proposed in regard to estimations showing that exposures at this dose are sufficient to decrease ARGS level and are similar to those at which an effect on cartilage is observed in animal models.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

The safety for use during pregnancy has not been established. No data have been generated in nursing women and no data are available on teratogenicity and excretion in milk. Therefore as

precaution, women of child-bearing potential (WOCBP) should be excluded from clinical studies with S201086/GLPG1972.

3. STUDY OBJECTIVES AND PURPOSE

Objectives:

The objectives of this study are to evaluate the efficacy and safety of 3 doses of S201086/GLPG1972 compared to placebo in patients with knee OA.

The primary objective of the study is to demonstrate the efficacy of at least one dose (among 3 doses) of S201086/GLPG1972 compared to placebo after 52 weeks of treatment in reducing cartilage loss measured by cartilage thickness using qMRI of the cMTFC of the target knee.

The secondary objectives are:

To assess the safety and tolerability of 3 doses of S201086/GLPG1972.

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on:

- the proportion of "structural progressors*" based on cartilage thickness using qMRI of the cMTFC of the target knee
- pain, function, and stiffness measured with WOMAC
- pain measured with a 100-mm visual analog scale (VAS)
- patient global assessment (PGA) of disease activity measured with 100-mm VAS
- reduction of cartilage loss measured by cartilage thickness using qMRI of the total tibiofemoral compartment (tTFC) of the target knee
- JSW measured by x-ray

**defined as patient who had at least 8% cartilage loss in the cMTFC between baseline and W052.*

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 28 and 52 weeks of treatment on bone area using qMRI of the medial femoral condyle surface of the target knee.

To assess the pharmacokinetics of S201086/GLPG1972 (and metabolite[s] if applicable).

To assess efficacy of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on analgesic consumption.

Exploratory objectives are:

To assess effect of 3 doses of S201086/GLPG1972 versus placebo after 52 weeks of treatment on:

- ARGS biomarker
- cartilage and bone degradation biomarkers

To assess influence of genes sequences or expression on patient's response to treatment

To evaluate a dose-response relationship between the 3 doses of S201086/GLPG1972.

To assess the relationship between exposure and pharmacodynamics (as safety and efficacy).

4. STUDY DESIGN

This study is a phase 2, international, multi-regional, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study of 52 weeks.

4.1. Endpoints

The primary efficacy endpoint:

The change from baseline to W052 in cartilage thickness of the cMTFC of the target knee: qMRI.

Secondary efficacy endpoints:

- Proportion of structural progressors* at W052 based on cartilage thickness of the cMTFC of the target knee: qMRI
- The change from baseline to W052 in WOMAC subscales scores of the target knee for pain, function, and stiffness
- The change from baseline to W052 in pain of the target knee: 100-mm VAS
- The change from baseline to W052 in PGA of disease activity of the target knee: 100-mm VAS
- The proportion of Outcome Measures in Rheumatology (OMERACT)-OARSI responders** at W052: defined according to WOMAC and PGA
- The change from baseline to W052 in cartilage thickness of the tTFC of the target knee: qMRI
- The change from baseline to W028 and to W052 in bone area of the medial femoral condyle surface of the target knee: qMRI
- The change from baseline to W052 in JSW of the target knee: X-Ray
- Pain: analgesic consumption at every visit up to W052

** defined as patient who had at least 8% cartilage loss in the cM- TFC between baseline and W052.*
*** based on OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for OA clinical trials revisited Pham et al. 2004. Defined according to WOMAC and patient's global assessment as a patient who had:*

- *high improvement in pain or in function ≥ 50% and absolute change ≥ 20 or*
- *moderate improvement in at least 2 of the 3 following:*
  - *Pain ≥ 20% and absolute change ≥ 10*
  - *Function ≥ 20% and absolute change ≥ 10*
  - *Patient's global assessment ≥ 20% and absolute change ≥ 10.*

Other secondary endpoints

Safety:

The safety and tolerability assessed by the incidence of adverse events (AEs), changes over time in safety parameters, and incidence of abnormal safety parameters throughout the study.

Pharmacokinetics:

- Pharmacokinetics of S201086/GLPG1972 (and metabolite[s] if applicable)

Exploratory endpoints:

- Biomarker of drug activity:
  - The change from baseline to each post baseline (W004, W012, W028, and W052) visits in ARGS concentration (serum)
  - The value at baseline and at each post baseline (W004, W012, W028, and W052) visits in ARGS concentration (serum)
- Biomarkers of cartilage (uCTX-II) and bone (sCTX-I, uCTXIα) degradation (serum and/or plasma and/or urine):
  - The change from baseline to each post baseline (W004, W012, W028, and W052) visits.
  - The value at baseline and at each post baseline (W004, W012, W028, and W052) visits.

  This list of biomarkers could be updated according to markers that may appear in the literature in the coming years.
- Optional genomic analysis of DNA/RNA.

4.2. Experimental design

4.2.1. Study plan

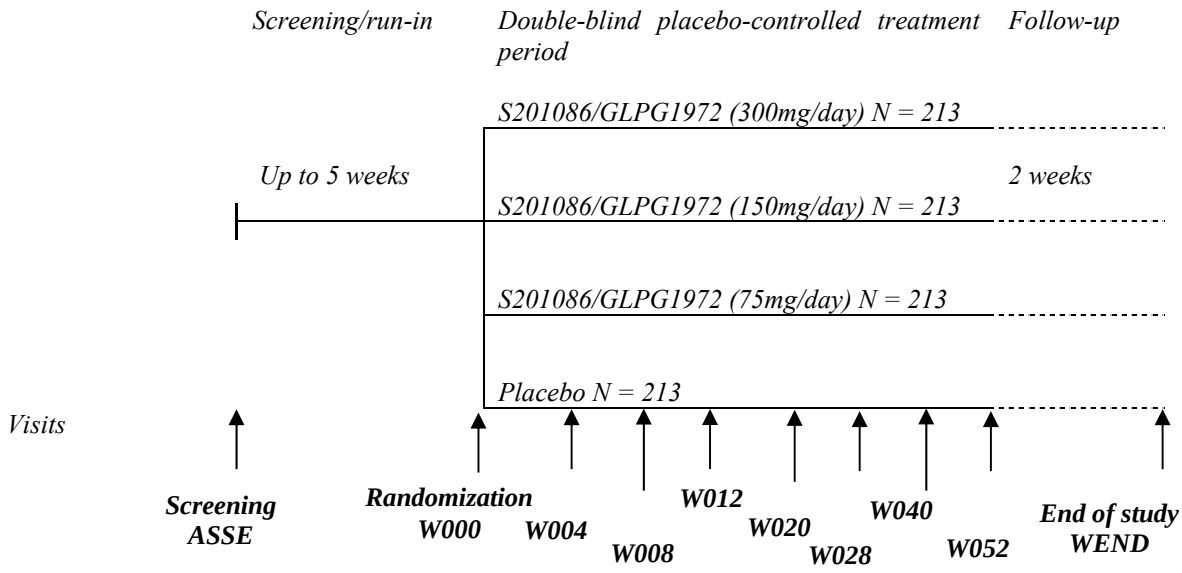
The expected duration of patient participation will be 61 weeks maximum.

The study is divided into the following periods:

- An up to 5-week **screening period** without study treatment from screening visit (ASSE) to inclusion visit (W000). The screening period (up to 5 weeks) will allow enough time to obtain results from X-ray examination, ECG, laboratory examination, and to perform the baseline qMRI (before IMP intake).
- A **double-blind treatment period** of 52 weeks (from W000 to W052 visit). Eligible patients will be included and randomly assigned to receive 75 mg/day, 150 mg/day or 300 mg/day S201086/GLPG1972, or matching placebo on a 1:1:1:1 ratio.
- A 2-week **follow-up period (WEND)** (from W052 or prematurely withdrawn to WEND): each patient must have a study end visit 2 weeks after completed or discontinued the study (definitely stopping study treatment), unless the patient withdraws consent.

The study plan is shown in Figure (4.2.1) 1.

Figure (4.2.1) 1 – Study plan



The study initiation is defined as the date of the first visit of the first patient.

End of Trial is defined as the date of the last follow-up visit of the last patient (including a contact phone), or the date of the last contact attempt if the last patient is declared lost to follow-up.

4.2.2. Investigation schedule

Table (4.2.2) 1 describes the measurement of efficacy and safety assessed during the study.

Table (4.2.2) 1 - Investigation schedule

	Screening ASSE (up to 5w)	Inclusion W000	W004 (+/-5d)	W008 (+/-5d)	W012 (+/-5d)	W020 (+/-7d)	W028 (+/-7d)	W040 (+/-7d) (end of morning or afternoon visit)	W052 (+/-7d)	*Premature withdrawal (WD)*	End of study WEND (2w+/-7d)
Informed consent	X										
Inclusion /exclusion criteria	X	X									
Demographics and Height	X										
Relevant medical / surgical history	X										
Previous and concomitant treatments[1]	X	X	X	X	X	X	X	X	X	X	X
IWRS[2]	X	X	X	X	X	X	X	X		X	
Allocation of IMP		X	X	X	X	X	X	X			
Compliance			X	X	X	X	X	X	X	X	
Efficacy measurements											
Primary qMRI (centralised)		X[3]					X		X	X[4]	
Secondary											
WOMAC		X			X		X	X	X	X	
VAS (pain) (ePRO)	X[5]	X	X	X	X	X	X	X	X	X	X
VAS (PGA) (ePRO)		X			X		X	X	X	X	
X-ray (centralized)	X[6]								X	X[7]	
Analgesic consumption		X	X	X	X	X	X	X	X	X	X
Safety measurements											
Adverse events[8]	X	X	X	X	X	X	X	X	X	X	X
Physical examination including knees	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X			X		X		X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examinations: ✓ Hematology/biochemistry (central) ✓ Urinalysis (local)	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (centralized)	X[9]	X[9]	X				X		X	X	X
Pharmacokinetics											
Blood samples			X[10]		X[10]		X[11]	X[12]	X[10]	X[10]	
Biomarkers											

✓ARGS (serum): blood sample		X	X		X		X		X	X	X
✓Cartilage/bone Markers: - blood sample (serum and plasma) - urine sample		X X	X X		X X		X X		X X	X X	X X
Optional measurements Blood sample (RNA) Blood sample (DNA)		X X							X		

1. *Previous treatments are all treatments stopped within 6 months before screening visit; concomitant treatments are treatments ongoing at screening visit as well as new treatments initiated during the study*
2. *IWRS connection to obtain patient's number (ASSE), randomization of patient following confirmation of inclusion eligibility, treatment allocation at W000, W004, W008, W012, W020, W028 and W040 and in case of premature withdrawal*
3. *The qMRI at baseline should be performed after getting results of screening criteria (lab, ECG, X-Ray) and before the first IMP intake*
4. *To be performed only if the previous qMRI (W000 or W028) is done ≥ 2 months before the premature withdrawal (time window between 2 qMRI)*
5. *Assessment of pain on both knees at screening visit only. Further assessments of pain will be performed on the target knee only*
6. *X-Ray on both knees at the screening visit only. Further assessment will be performed on the target knee only*
7. *To be performed only if the previous X-Ray (W000) is done more than 9 months before the premature withdrawal (time window between 2 X-Ray)*
8. *See section 8.9 for reporting methods*
9. *ECGs should be triplicate at ASSE and W000*
10. *Pre dose PK samples means that patients have to take their IMP at the site*
11. *Pre dose PK sample + one post dose PK sample (interval 2-4h post dose). Patients have to take their IMP at the site*
12. *One post dose PK sample (interval 4-8h post dose). Patients have to take their IMP at least 4 hrs. before sampling and report the time of dosing to the study staff*

For further practical details, methods of measurement are provided in sections 7, 8 and 9.

4.3. Measures to minimize bias

- This is a double-blind, placebo-controlled study.
- The appearance and taste of the tablets will be the same for all study drugs, in order to protect the blinding with regard to the patients and the investigators.
- The treatment, S201086/GLPG1972 75 mg/day, 150 mg/day, 300 mg/day or matching placebo, will be assigned at randomized visit (W000) by a balanced (1:1:1:1), non-adaptive randomization, with stratification by region (Asia and Rest of the World).
- Treatment randomizations and allocations will be centralized by Interactive Web Response System (IWRS). The structure responsible for designing and constructing the randomization lists in blind will be the biostatistics department of I.R.I.S.
- As S201086/GLPG1972 may have an effect on serum ARGS level as well as on serum/plasma/urine cartilage and bone biomarkers, no results will be communicated to the investigator or the Sponsor in order to avoid any unblinding during the study. Results will be transferred to the I.R.I.S. Data Management department only after clinical database lock in order to avoid any unblinding during the study.
- The following measures (centralized) will be taken to optimize the homogeneity and the reliability of the study data:
  - MRI and X-Ray reading will be centralized. The CRO in charge of medical imaging management will organize the training and validation of sites participating in the study and will perform imaging quality controls and X-ray reading, and manage the MRI transfer to the central reading service provider.
  - ECG reading and interpretation will be centralized throughout the study by a CRO. All study centers will be supplied with an ECG device by the CRO central reading,
  - Laboratory parameters will be assessed centrally by a CRO.
- Pain VAS, and PGA VAS will be recorded using electronic patient reported outcome (ePRO).
- Samples for pharmacokinetic analysis will be sent to the central laboratory and transferred to the assay center. The assay center in charge of S201086/GLPG1972 measurement in biological matrices will be provided with the treatment codes so that only samples from patients being treated with S201086/GLPG1972 will be assayed (patients under active treatment).
  The results of the S201086/GLPG1972 plasma concentration will be transferred from assay center to the I.R.I.S. pharmacokinetic department before the clinical database is locked (recoded patient number). In order to prevent a blind break, administration and sample times will only be recorded on the requisition form (not on the electronic case report form [eCRF]). The central laboratory will capture the data of the requisition form and will calculate the time after dose. Real time after dose will be transferred to the assay center for analyses. PK results from assay center and requisition form data from the central laboratory will be transferred to the I.R.I.S. Data Management department only after blind broken.

4.4. Data and safety monitoring board

A Data and Safety Monitoring Board (DSMB) will be put in place in order to independently review the available safety data at regular pre-specified time points. The functioning of this DSMB is specified in a separate DSMB charter.

5. INCLUSION OF PATIENTS

5.1. Inclusion criteria

All patients included should present the following characteristics:

1. Male patients or female patients of non-childbearing potential.
   Note: Female patients will be considered of non-childbearing potential if they are either surgically sterile or postmenopausal (at least 12 consecutive months of amenorrhea in the absence of other biological or physiological causes).
2. Age between 40 to 75 years (both inclusive).
3. Body weight > 40 kg.
4. Body mass index (BMI) < 40 kg/m^2.
5. Diagnosed for knee OA based on the clinical and radiological criteria of the ACR (documented diagnosis), *i.e.*:
   a- Knee pain
   b- *and*, at least one of the following:
      - age more than 50 years
      - morning stiffness < 30 minutes duration
      - crepitus on active motion
   c- and, presence of osteophytes
6. History of knee pain for at least 6 months and on the majority of days (> 50%) during the preceding month.
7. Symptom severity defined by a pain ≥ 40 mm and ≤ 90 mm on a 100 mm VAS at screening and inclusion visits (at screening <u>both</u> knees should be assessed for pain and at least one knee should fulfill pain severity defined on this criterion).
8. Documented need for symptomatic as needed-treatment for OA in the target knee with systemic non-steroidal anti-inflammatory drugs (NSAIDs) and/or other analgesics
9. Disease stage based on a fixed flexion weight-bearing X-ray of the target knee* and central read out of:
   a. Predominant medial compartment radiographic disease
   b. KL grade 2 or 3
   c. And OARSI grade 1 or 2 medial tibiofemoral joint space narrowing (JSN)

*****The target knee (right or left) to be followed-up throughout the study will be chosen as follows:

- If both knees fulfill the clinical screening criteria (as described in Section 5.1) and radiological inclusion criteria, the knee to be chosen should be the most clinically painful one (Higher VAS score at screening).
- If both knees are equally painful, the most severely affected knee on X-ray (higher KL score); in case of similar KL scores, the higher JSN score will be selected.
- If both knees are equally painful and display the same radiological scores, the choice should be left to the investigator's discretion.

10. Informed consent obtained as described in section 13.3 of the protocol.

5.2. Exclusion criteria

11. Unlikely to cooperate in the study.
12. Participation in another interventional study within 3 months before screening; participation in non-interventional registries or epidemiological studies is allowed.

13. Re-screened patient.
14. Patient unable to understand the study.
15. Poor compliance anticipated by the investigator.
16. Investigator or other study staff or related thereof who is directly involved in the conduct of the study.
17. Severe clinical knee malalignment according to the investigator.
18. Knee prosthesis already implanted (< 1 year) or not well-tolerated (contralateral side).
19. Knee prosthesis already foreseen within the study period (whichever side).
20. Hip prosthesis recently implanted (< 1 year) or foreseen within the study period (whichever side).
21. Previous osteotomy on the inferior limbs (whichever side).
22. Surgical operation on the target knee within the 12 months prior to the screening visit or planned during the study period.
23. Arthroscopy of the target knee within the 6 months prior to the screening visit or planned during the study period.
24. Other pathologies affecting the knee such as: septic arthritis, inflammatory joint disease, gout, major chondrocalcinosis (pseudogout), Paget's disease of the bone, ochronosis, acromegaly, haemochromatosis, Wilson's disease, rheumatic symptoms due to malignancies, primary osteochondromatosis, osteonecrosis, osteochondritis dissecans, hemophilia, etc.
25. Generalized pain syndrome, for example fibromyalgia.
26. Chronic oral corticosteroid therapy within one month prior to enrolment into the study other than stable doses of ≤ 7.5 mg daily prednisolone or equivalent.
27. Knee corticosteroid or hyaluronic acid intra-articular injections in the previous 3 months.
28. Use of medications with MMP-inhibitory properties (*i.e.* Tetracycline or structurally related compounds) during the 3 months prior to the screening visit.
29. Bisphosphonates, Denozumab, Teriparatide and Strontium ranelate use (in oral or injectable form) in the previous 12 months
30. Use of other unapproved drugs for osteoarthritis treatment during the 3 months prior to the screening visit.
31. Chronic use of strong opioids (see list under section 6.6 on symptomatic drugs).
32. Any contraindication to MRI according to local MRI guidelines, including the inability to undergo a knee MRI exam because of inability to fit in the scanner or knee coil.
33. Non-pharmacological standard of care (Physiotherapy, electrotherapy, etc...) if not stable in the 4 weeks prior to the screening visit.
34. Severe or unstable disease of any type that could interfere with safety and efficacy assessments (*e.g.*, uncontrolled cardiovascular, pulmonary, infectious, severe immune-deficiency, autoimmune, renal, hepatic, gastro-intestinal, endocrine, blood disorders) according to investigator's judgment
35. History of malignancy in the past 5 years, with the exception of: basal cell carcinoma, resected cutaneous squamous cell carcinoma in situ, prostate cancer in situ with a normal prostate-specific antigen post treatment, cervical carcinoma in situ, gastric cancer in situ, colon cancer in situ adequately treated with no significant progression over the past 2 years.
36. Class III or class IV Heart failure according to the New York Heart Association (NYHA) classification.
37. Known moderate to severe renal impairment; *i.e.*, estimated Glomerular Filtration Rate (GFR) < 45 mL/min/1.73 m^2 (Modification of the Diet in Renal Disease [MDRD] formula)
38. Clinically significant abnormalities detected on a 12-lead ECG performed at screening visit of either rhythm or conduction (*e.g.*, QT interval corrected for HR according to Fridericia's formula [QTcF] interval > 450 ms for males and > 470 ms for females, bradycardia with

HR < 50 bpm, measured and stable PR > 280 ms, or second or third degree Atrio-Ventricular Block, complete left branch block)

39. Known severe hepatic impairment (*i.e.*, cirrhosis, active liver disease) or known liver enzymes abnormalities such as:
    - Aspartate aminotransferase (AST) and/or ALT values > 2 x upper limit of normal (ULN)
    - Alkaline phosphatase (ALP) > 3 x ULN,
    - Total bilirubin > 1.5 x ULN (except in case of Gilbert syndrome)
40. Positive for hepatitis B surface antigen (HBs), anti-hepatitis C virus (HCV) antibodies or anti-human immunodeficiency virus (HIV) antibodies
41. Severe malabsorption according to investigator's judgment.
42. Unexplained significant weight loss (> 10% of body weight within the last year).
43. Alcohol abuse or drug abuse or addiction according to investigator's judgment.
44. Hypersensitivity to the active substance or to any of the excipients.

5.3. Contraception

Within the frame of this study, as the effect of S201086/GLPG1972 on sperm in man is unknown, male clinical study patients and **their female partners of child-bearing potential must use highly effective contraception** (as described in the informed consent form) **in combination with a barrier contraceptive** to prevent pregnancy and to avoid the risk of exposure of the embryo or fetus during the study and up to 12 weeks after the last dose received.

Male patients agree to not donate sperm from the time of first study drug intake during the study and until 12 weeks after the last study drug intake.

5.4. Discontinuation of the study

5.4.1. Premature discontinuation of the study or temporary halt

This study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause.

After having informed the national coordinators, the sponsor or the institutional review board (IRB)/independent ethics committee (IEC) or the Regulatory Agencies may terminate the study before its scheduled term. Two copies of the written confirmation will be dated and signed by the coordinators. The IRB/IECs and Regulatory Agencies will be informed according to local regulations.

If the study is prematurely discontinued, the patients still included in the study should be seen as soon as possible and the same assessments as described in Section 5.5 should be performed.

The premature withdrawal visit should be notified via IWRS (refer to investigation schedule Table (4.2.2) 1).

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, the DSMB, the IRB/ IEC and Regulatory Agencies.

5.4.2. Discontinuation of the study in the event of objective reached

Not applicable

5.5. Patient withdrawal

5.5.1. Withdrawal criteria

A patient may be discontinued from the clinical study at any time without the patient's consent if the investigator or sponsor determines that it is not in the best interest of the patient to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the patient will complete the premature withdrawal (WD) visit and follow-up visit (WEND) for safety assessments.

Treatment with S201086/GLPG1972 must be discontinued by the investigator and the patient must be withdrawn from the clinical study (preferably after discussion with the medical monitor, who may consult and must inform the sponsor's study physician) for any of the following conditions:

- Life-threatening adverse event (AE) or a SAE that places the patient at immediate risk.
- Confirmed pregnancy
- Any ECG and/or laboratory parameter abnormalities such as:
  - QTcF > 500 ms on at least two separate ECGs
  - Increase in liver function tests:
    1. ALT or AST > 8x ULN (discontinue the treatment immediately),
    2. ALT or AST > 5x ULN confirmed at retest for more than 2 weeks,
    3. ALT or AST > 3x ULN and (total bilirubin > 2x ULN or international normalized ratio [INR] > 1.5),
    4. ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%),
    5. Presence of evocative clinical symptoms such as jaundice.

  If any of the above laboratory abnormalities is detected, retesting is prompted (for central laboratory) and resampling of the patient should be performed preferably within 48 h after laboratory results are received by the investigator.

  Based on the re-test results, it should be determine together with medical monitor if the discontinuation criteria are confirmed. If confirmed, the patient must be withdrawn from the clinical study.

  In any case of liver toxicity, additional investigations are needed (such as: assessment of alcohol or recreational drugs intake, hepatitis infection, etc...)

- Any AE or any condition incompatible with continuation of the investigational medicinal product (IMP) according to the judgment of the investigator

The investigator may also decide to stop the treatment with S201086/GLPG1972 (preferably after consultation with the sponsor's study physician) for any of the following reasons:

- Use of concurrent therapy that was not permitted
- Noncompliance with the IMP treatment
- Noncompliance with the clinical study procedures
- Serious or severe AEs
- Worsening of disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study

Patients will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a patient's participation in the clinical study may terminate at his/her request without prejudice to his/her future medical care. The patient will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the WD visit and follow-up visit (WEND) for safety assessments, but will not be obliged to do so.

Patients who drop out before the first administration of the IMP will be replaced. Patients who stop taking IMP for any reason will not be replaced.

The sponsor has the right to terminate the clinical study at any time in case of safety concerns or if special circumstances concerning the IMP or the company itself occur, making further treatment of patients impossible. In this event, the investigators and relevant authorities will be informed of the reason for clinical study termination.

Information to be collected during the last visit of these patients is listed in Section 5.5.2. These follow-up assessments are included to ensure the efficacy and safety evaluation of all patients who received the IMP.

5.5.2. Procedure

- In the case of premature withdrawal from the study due to an AE, the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see Section 8.9). This information is recorded in that part of the eCRF which concerns adverse events. If the investigator cannot collect the information from a visit, every effort must be made ensuring the follow-up of the patient.
- If the study is stopped / IMP is discontinued as a result of an event requiring immediate notification, the procedure described in Section 8.9.2.4 has to be implemented.

The actions to be taken after the IMP discontinuation are described in Section 6.5.

5.5.3. Lost to follow-up

When the investigator has no news of the patient, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc....), to establish the reason for the discontinuation of IMP and to suggest the patient comes to an end-of-study visit. If all these attempts to contact the patient fail, the investigator can then declare the patient "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PATIENTS

6.1. Study products and blinding systems

6.1.1. Products administered

IMPs (also mentioned as study drug in this protocol) in this study are the study drug S201086/GLPG1972 (at dose of 75 mg, 150 mg or 300 mg) and matching placebo.

The study drug S201086/GLPG1972 will be provided as film-coated tablets for oral use, containing 75 mg S201086-1/G504572 each (S201086-1/G504572 is the compound code for S201086/GLPG1972). The placebo will be provided as matching film-coated tablets for oral use.

The oral tablets will be packaged in polyvinylchloride (PVC)/aluminum (Alu) blisters, which are grouped in a carton box.

Table (6.1.1) 1 provides a description of the IMP(s).

Table (6.1.1) 1 – Description of the IMPs

	S201086/GLPG1972 75 mg	**Placebo**
Pharmaceutical form	Film-coated tablet	Film-coated matching tablet
Unit dosage	75 mg	-
Appearance, color	orange	orange
Composition*	Lactose monohydrate	Lactose monohydrate

**excipient with known effect*

Table (6.1.1) 2 provides a description of the packaging of the IMP

Table (6.1.1) 2 – Description of packaging

Number of units of the pharmaceutical form per primary packaging	28 tablets of S201086/GLPG1972 75 mg and/or placebo per blister
Number of primary packaging per secondary packaging	5 blisters per small box

The labeling of packages complies with the regulatory requirements of each country involved in the study.

6.1.2. IMP management

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to section 6.3), accountability and collection are the responsibility of the investigator, delegated person of the study team and/or pharmacist of the medical institution.

Destruction of the IMP is the responsibility of the sponsor and the person responsible for the IMP management.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management.

A certificated destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. The practical procedures for destruction of unused IMP will be defined by the sponsor and adapted to the center. An IMP collection and destruction form will be completed before the shipment of IMP to destruction. Destruction of IMP may be possible (after drug accountability and sponsor authorization) when the product has been used, has expired or after at least the last visit of the last treated patient. The IMP should be stored in a secure area with restricted access.

IMP management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete all the documents provided by the sponsor concerning IMP management in real time (therapeutic unit tracking form or an equivalent document, therapeutic unit (TU) label collection form). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfill.

The investigator and/or the pharmacist of the medical institution should only use the IMP provided for the patients involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported to section 8.9.2.4.2 (special situations), and to the IWRS. The investigator will notify of all complaints set out by a patient (appearance…).

In the event of advanced return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre. On receipt of the letter, the investigator and/or the pharmacist will identify the patients in possession of the IMP at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document, and will contact them immediately.

6.1.3. Management of blinding systems

The patient treatment code should only be broken in case of emergency where the further treatment of the patient is dependent on the treatment he or she is receiving.

In the cases where the blind needs to be broken by the investigators for imperative justified medical reason, a centralized decoding system integrated with the IWRS is adopted for the study. No sealed envelopes will be used.

The centralized decoding procedure will be performed by the investigators by contacting the IWRS. The system is available 24 hours a day, 7 days a week. The procedure to be followed by the investigator or authorized person is detailed in the IWRS manual.

If IWRS is not available, the helpdesk of the IWRS will be contacted by phone.

For all countries except US:

Additionally, decoding will be possible by calling the Emergency Phone Number of I.R.I.S. (+33 1 55 72 60 00) 7/7d and 24/24h) to reach the Emergency Permanency that will have a sealed decoding list not available to other I.R.I.S. personnel during the study. A code list will be kept in a safe place by the I.R.I.S. Clinical Supplies Coordinating Department and will be accessible to any person authorized to unblind.

6.2. IMPs administered

No IMPs will be administered during screening and follow up periods.

From the day of inclusion until the W052 Visit, the patient will take four (4) tablets orally once a day with a glass of water preferably in the morning (at the same time), corresponding to:

- S201086/GLPG1972 75 mg/day: 1 tablet of 75 mg + 3 matching tablets of placebo,
- S201086/GLPG1972 150 mg/day: 2 tablets of 75 mg + 2 matching tablets of placebo,
- S201086/GLPG1972 300 mg/day: 4 tablets of 75 mg,
- 4 matching tablets of placebo.

During visits, the IMP will be taken at the site (during the visit) except for W040 (for PK sampling) where IMP will be taken at home and the exact intake time will be reported.

6.3. IMPs dispensing

Investigator and/or the pharmacist of the medical institution and / or a designated person from their study team will use the IWRS, as described in the IWRS manual, to perform the following actions:

- To create the patient number at ASSE visit,
- To randomize the patient and allocate the treatment at W000 visit,
- To allocate treatment at W004, W008, W012, W020, W028, and W040 visits,
- To register "Premature withdrawal" if applicable.

The IWRS manual will detail all instructions for randomization and allocation of the treatment. The IMP is dispensed at W000, W004, W008, W012, W020, W028 and W040 visits.

The detachable portion of the label on the IMP box must be stuck by the investigator or a delegated person on an IMP label collection form or on the prescription form where the IMPs are dispensed by a pharmacist.

6.4. IMP compliance

The number of tablets dispensed and the number of tablets returned by the patient are to be counted by the investigator or a designated person from his/her team and recorded in the electronic case report form and therapeutic unit tracking form, or an equivalent document.

If the patient did not bring back all blisters dispensed at the previous visit, the investigator must estimate the number of IMP units taken by the patient since the previous visit, by questioning him/her and must document the reason in the medical file.
Compliance will be assessed at each visit or in case of premature withdrawal.

The compliance will be assessed from the method described above and from the questioning of the patient.

6.5. Discontinuation of the IMP

After the discontinuation of the IMP, the patients' treatment is left to the physician's discretion. As the study drug is not on the market, it will not be available.

Specific rules may be followed in some countries according to local regulation.

6.6. Previous and concomitant treatments

Previous treatments are all treatments stopped within 6 months before screening visit; concomitant treatments are treatments ongoing at screening visit as well as new treatments initiated during the study.
Previous and concomitant treatment (prescriptions or over-the-counter medications) must be reported in the eCRF. Reported information will include a description of the type of the drug, treatment period, dosing regimen, route of administration and its indication. Any change in dosage must also be reported in the Concomitant Treatments eCRF section. Data on concomitant medication will be collected up to the last follow-up visit, even after withdrawal of a patient.

Treatment prohibited before and during the study:

Type of treatment			**Time since last administration before screening**
Symptomatic drugs	oral	Corticosteroids > 7.5 mg/d Prednisolone or equivalent	1 month
	injection	Intra-articular corticosteroids Intra-articular hyaluronic acid	3 months
	oral	Drugs with potential effect on cartilage *e.g.* Tetracycline or structurally related compounds	3 months
Drugs with an effect on subchondral bone	oral or injection	Bisphosphonates Denozumab Teriparatide Strontium Ranelate	12 months
Strong opioids		*Short-acting, More Potent* Morphine sulfate Codeine sulfate Oxycodone (with or without aspirin, acetaminophen, ibuprofen) Hydromorphone Meperidine hydrochloride Fentanyl citrate transmucosal Oxymorphone *Long-acting* Morphine sulfate sustained release Fentanyl transdermal Levorphanol tartrate Oxycodone HCL controlled release Methadone	Chronic use
Possible drug/drug interaction (CYP3A4, 2D6, 2C19 and BCRP)*		**CYP3A4 inducers:** Avasimibe, Bosentan, Carbamazepine, Modafinil, Nafcillin, Phenytoin, Rifampin, St. John‘s wort <u>Antiviral and anticancer drugs:</u> Efavirenz, Enzalutamide, Etravirine, Mitotane **CYP3A4 inhibitors:** Aprepitant, Casopitant, Ciprofloxacin, Clarithromycin, Conivaptan, Diltiazem, Dronedarone, Erythromycin, Fluconazole, Grapefruit juice, Isavuconazole, Itraconazole, Ketoconazole, Mibefradil, Nefazodone, Netupitant, Posaconazole, Schisandra sphenanthera, Telithromycin,	7 Days

		Tofisopam, Troleandomycin, Voriconazole, Verapamil Antiviral and anticancer drugs: Amprenavir, Atazanavir, Boceprevir, Crizotinib, Darunavir/Ritonavir, Faldaprevir, Fosamprenavir, Idelalisib, Imatinib, Indinavir, Lopinavir, Nelfinavir, Nilotinib, Saquinavir, Telaprevir **Dual CYP3A4 / CYP2D6 inhibitors** Telithromycin, Dronedarone, Diltiazem, Verapamil, Amiodarone** Antiviral and anticancer drugs: Lopinavir/ritonavir, Ritonavir, Imatinib **BCRP substrates**: Hematoporphyrin, Methotrexate, Pitavastatine, Rosuvastatin, Sulfasalazine Antiviral and anticancer drugs: imatinib, lapatinib, topotecan **CYP2C19 substrates**: S-mephenytoin	

Treatment authorized during the study with particular conditions for use:

Type of treatment			
Symptomatic drugs	oral	Glucosamine (sulphate or others) Chondroitin sulfate	Under condition of stable dosing for at least 3 months before screening and during the study
		diacerein	
		Avocado/soybean unsaponifiables	

*https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

** Due to long half-life, Amiodarone is forbidden before and during the study.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table (4.2.2) 1.

7.2. Methods and measurement times

7.2.1. Medical imaging

Before their participation in the study CL2-201086-002/GLPG1972-CL-201, all centers will receive a specific training/qualification coordinated by the CRO in charge of medical imaging management. In addition, this CRO will be in charge of:

- Imaging (MRI and X-ray) reception and quality control (QC),
- X-ray reading
- MRI transmission to the MRI reader, and
- Imaging (MRI and X-ray) data transfer to the Sponsor.

The aim is to ensure standardized and appropriate acquisition and assessments of medical imaging.

- **qMRI:**

quantitative MRI of the target knee will be performed at W000 (inclusion), W028 and W052 visits, and at the withdrawal visit (WD) if the time window between WD and the previous qMRI (W000 or W028) is ≥ 2 months.
If a patient withdraws from the study after at least 2 months after W000 or after W028, every effort should be made to schedule for a final qMRI acquisition in order to have a final measurement available.

All MRI images will be transmitted to the medical imaging management CRO. If a scheduled qMRI fails QC, one repeat qMRI is allowed. After passing QC, qMRI images will be sent to the medical image analysis service provider for central reading and analysis (coded data). The qMRI acquisition technique, image tracking and management and reading methods will be described in specific documents that will be available before the center initiation visit.

In addition, first patient per site will be scanned twice with repositioning at both baseline (W000 visit) and at W052 visit for quantitative measurement to calculate the within study variability.

All patient results will be returned to the site following finalization of the clinical study report.

- **Radiography (X-ray):**

A weight-bearing X-ray of the knee (both knees at ASSE and the target knee at W052) will be performed in all patients. If a patient withdraws from the study > 9 months after initial X-ray, every effort should be made to schedule for a final X-ray of the target knee in order to have a final measurement available.
All X-rays will be transmitted to the medical imaging management CRO. If a scheduled X-ray fails QC, one repeat X-ray is allowed (for each knee at the screening visit and for the target knee at every visit when X-ray is scheduled). After passing QC, images will be analyzed by central readers (coded data). A scoring according to the KL grading and OARSI JSN grading will be performed on both knees at screening visit (ASSE) only and transmitted within a specific

short timeframe to the investigational site in order to include or exclude the patients. The minimal JSW will be measured using a semi-automated computerized method according to a standardized method detailed by a separate technical protocol.

The X-ray acquisition technique, images tracking and management and reading methods will be described in specific technical documents that will be available in time before the center initiation visit.

All patient results will be returned to the site following finalization of the clinical study report.

7.2.2. WOMAC for measurement of pain, function and stiffness (Appendix 2)

The WOMAC index score will be assessed on site at W000, W012, W028, W040, W052 and if applicable at the withdrawal visit (WD).

WOMAC is a questionnaire designed to assess health status and health outcomes in patients with osteoarthritis of the knee. The questionnaire contains 24 questions targeting areas of pain (5 questions), stiffness (2 questions) and physical function (17 questions). The questionnaire is self-administered by the patient and can be completed in less than 5 minutes. It refers to the 48h period prior to assessment and will be completed before the clinical examination, preferably in the waiting room.
The WOMAC will be recorded by paper and data will be entered by the investigator or a delegate person on eCRF.

7.2.3. VAS for pain intensity (Appendix 3)

After the choice of the target knee to be followed throughout the study has been made by the investigator and explained to the patient, the pain intensity will be assessed during each visit (ASSE on both knees and W000, W004, W008, W012, W020, W028, W040, W052 and WEND on the target knee and if applicable at the withdrawal visit (WD)) by the patient him/herself by marking the level of pain on a 100-mm VAS. The scale should be completed before the clinical examination, with the patient being asked on the level he would rate the pain felt in the selected knee within the last 48 hours on a VAS.
The pain VAS will be recorded by ePRO. The questionnaire will be explained to the patient by the investigator (or a delegate person) and will be filled in by patients during the visits on an electronic device (e-PRO). Data entered by the patient will be sent to a central database via a secured transfer.

7.2.4. VAS for Patient Global Assessment of disease activity (PGA) (Appendix 4)

The PGA VAS will be assessed during the following visits: W000 (inclusion), W012, W028, W040, W052 and if at the withdrawal visit (WD) by the patient him/herself by marking the level of "Considering all the ways in which your knee osteoarthritis affects you, please rate on this 100 mm scale how well you are doing today" on a 100 mm VAS.
The PGA VAS will be recorded by an ePRO solution. The questionnaire will be explained to the patient by the investigator (or a delegate person) and will be filled in by patients during the visits on an electronic device (e-PRO). Data entered by the patient will be sent to a central database via a secured transfer.

7.2.5. Analgesic consumption

Drug analgesic consumption of the patient will be recorded on the eCRF at W000 (inclusion), W004, W008, W012, W020, W028, W040, W052, WEND and if applicable at the withdrawal visit (WD).

8. SAFETY MEASUREMENTS

All AEs and other situations relevant to the safety of the patients must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical study.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table (4.2.2) 1.

The safety will be assessed based on of the following information:

- AEs
- Physical assessment including knees
- Vital signs
    - After 5 min. in supine position assessed with automatic blood pressure monitoring (in case of equipment is supplied by the sponsor, equipment has to be used)
        - Systolic blood pressure (SBP) (mmHg)
        - Diastolic blood pressure (DBP) (mmHg)
        - Pulse Rate (bpm)
    - Body weight (kg)
- 12-lead-ECG: qualitative and quantitative ECG findings (HR, PR, QRS, QT, QTcF and [RR] intervals) (equipment supplied by the CRO in charge of ECG central reading). At ASSE and W000, ECG will be in triplicate.
- Biological laboratory examinations
    - Blood biochemistry includes ALT, AST, gamma glutamyltransferase (GGT), ALP, lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), total and conjugated bilirubin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, total protein, albumin, creatinine (with calculation of the GFR), urea, glucose, uric acid, sodium, potassium, chlorides, calcium, bicarbonate, C-reactive protein (CRP)
    - Hematology includes hemoglobin, hematocrit, erythrocytes, differential white cell count (leucocytes, basophils, eosinophils, neutrophils, monocytes, lymphocytes in absolute values), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets
    - Urinary dipstick (PH, red blood cells, white blood cells, glucose, proteins, ketones, bilirubin).

8.2. Methods and measurement times

Vital signs will be evaluated at ASSE, W000, W004, W008, W012, W020, W028, W040, W052, WEND and if applicable at the premature withdrawal visit (WD). Blood pressure will

be measured with Automatic Blood Pressure Monitor and SBP and DBP will preferably be measured on the same arm.

Body Weight will be evaluated at ASSE, W000, W012, W028, W052, WEND and if applicable at the premature withdrawal visit (WD).

Physical assessment including knees performed at ASSE, W000, W004, W008, W012, W020, W028, W040, W052, WEND and if applicable at the premature withdrawal visit (WD).

ECG will be performed at ASSE, W000, W004, W028, W052, WEND and if applicable at the premature withdrawal visit (WD). ECG device will be the same for all centers and will be supplied by the CRO in charge of ECG central reading. The ECG device should be used only for the study. All ECGs will be sent anonymized to the CRO for central reading.

Even if the 12-lead **ECG** reading and interpretation will be centralized, a local assessment of ECG is necessary for detection of medical urgencies and must be enclosed in the source data. Central reading reports overrule local reading for inclusion/exclusion/withdrawal criteria.

Laboratory examinations will be performed at: ASSE, W000, W004, W008, W012, W020, W028, W040, W052, WEND and if applicable at the premature withdrawal visit (WD).

Urinary dipstick will be performed locally. In case of abnormal urinary dipstick result, the investigator or his/her delegate will perform a quantitative urinalysis that will be done locally.

Laboratory results will be assessed by the investigator for clinical significance. In case of clinical significance, AEs/SAEs should be reported.

Laboratory tests analysis will be subcontracted to a central laboratory. The details for sampling, handling, storage and shipping of the samples will be described in a separate manual.

For the laboratory tests, it is recommended for patients to be fasted (if possible).

Additional safety investigations can be performed if deemed necessary should the investigator have a suspicion of any pathology requiring urgent medical intervention.

8.3. Definition of Adverse events

An AE is defined as any untoward medical occurrence in a patient participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the patient signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (*e.g.* run-in period) are also concerned).

An AE can therefore be:

- any unfavorable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity), including the studied pathology,

and detected during a study visit or at an additional examination or occurred since the previous study visit.

Of note:

- Any **hospitalization for social reasons, educational purpose** (*e.g.* learning of diabetes management by the patient) or routine check-up should not be considered as an adverse event and should not be reported in the eCRF.
- The following procedures, whether planned before the study or not, whether leading to a hospitalization or not, should be reported in the specific page **"Procedures not subsequent to an adverse event"** of the eCRF:
    - therapeutic procedures related to a non-aggravated medical history (*e.g.* cataract extraction not due to an aggravation of the cataract during the study, hemodialysis sessions related to a renal insufficiency not aggravated during the study),
    - prophylactic procedures (*e.g.* sterilization, wisdom teeth removal),
    - comfort procedures (*e.g.* cosmetic surgery),
    - control procedures of a pre-existing condition without aggravation (*e.g.* colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious adverse events

Any AE that at, any dose:

- results in death,
- is life-threatening[(1)],
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity[(2)],
- is a congenital anomaly/birth defect[(3)],
- is medically significant[(4)].

[(1)] Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[(2)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the patient to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the patient's body functions or structure, physical activity and/or quality of life.

[(3)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men) or during pregnancy that resulted in an adverse outcome in the child.

[(4)] Any event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of these outcomes (for example: edema or allergic bronchospasm that required intensive treatment at home, blood dyspraxia, convulsions that do not result in hospitalization, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgment to decide whether or not such an event requires expedited reporting to sponsor.

8.5. Definition of special situations

- Pregnancy of participant or partner of male participant in the study

- Other special situations:

- **Abuse of study drug**
  The persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects.
- **Misuse of study drug**
  Situations where the study drug is intentionally and inappropriately used not in accordance with the authorized product information.
- **Drug interaction with study drug**
  A situation in which the study drug interacts with another drug when both are administered together.
- **Food interaction with study drug**
  A situation in which food interacts with the study drug.
- **Medication error**
  An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.
- **Occupational exposure**
  An exposure to the study drug as a result of one's professional or non-professional occupation.
- **Overdose**
  The administration of a quantity of the study drug given per administration or cumulatively, which is above a certain dose as defined in the protocol **(>4 tablets/day).**
- **Product complaint or quality defect of study drug**
  Complaints arising from potential deviations in the manufacture, packaging, or distribution of the study drug.

8.6. Definition of Adverse event of special interest

At the time of writing this study protocol, no AE of special interest have been defined.

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (*i.e.* without delay and within 24 hours at the latest) to the sponsor if it is:

- a serious adverse event,
- a pregnancy and other special situations.

8.8. Classification of an adverse event (seriousness, severity, causality)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **severity** of the event as well as the **causal relationship** between an adverse event and the study drug. This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event (See Section 8.9.2.4.3).

The Seriousness should be evaluated according to international guidance (see definition Section 8.4, in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

The Severity of AEs should be graded using the modified Common Terminology Criteria for Adverse Events (CTCAE). If a CTCAE criterion does not exist, the investigator should use the

grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in the table below.

Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Fatal	Death-related AE

** Activities of Daily Living (ADL) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*
*** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

The causal relationship to the study drug or to the experimental procedure must be assessed when reporting the AE in the AE form. Only cases ticked "related" by the investigator, or judged by the sponsor as having a reasonable suspected causal relationship to the study drug, will be considered as suspected Adverse Drug Reaction.

The following decision table will be used by the investigator to report the causality assessment between the reported event and the investigational medicinal product.

Definitions	Relationship to report in eCRF
Unrelated: No relationship between the AE and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.	**NOT-RELATED**
Unlikely: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.	
Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake which could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.	**RELATED**
Probable: Event or laboratory test abnormality, with reasonable time relationship to drug intake. Event unlikely to be attributed to disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.	
Certain: Event or laboratory test abnormality, with plausible time relationship to drug intake which cannot be explained by disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (*i.e.*, an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if necessary.	

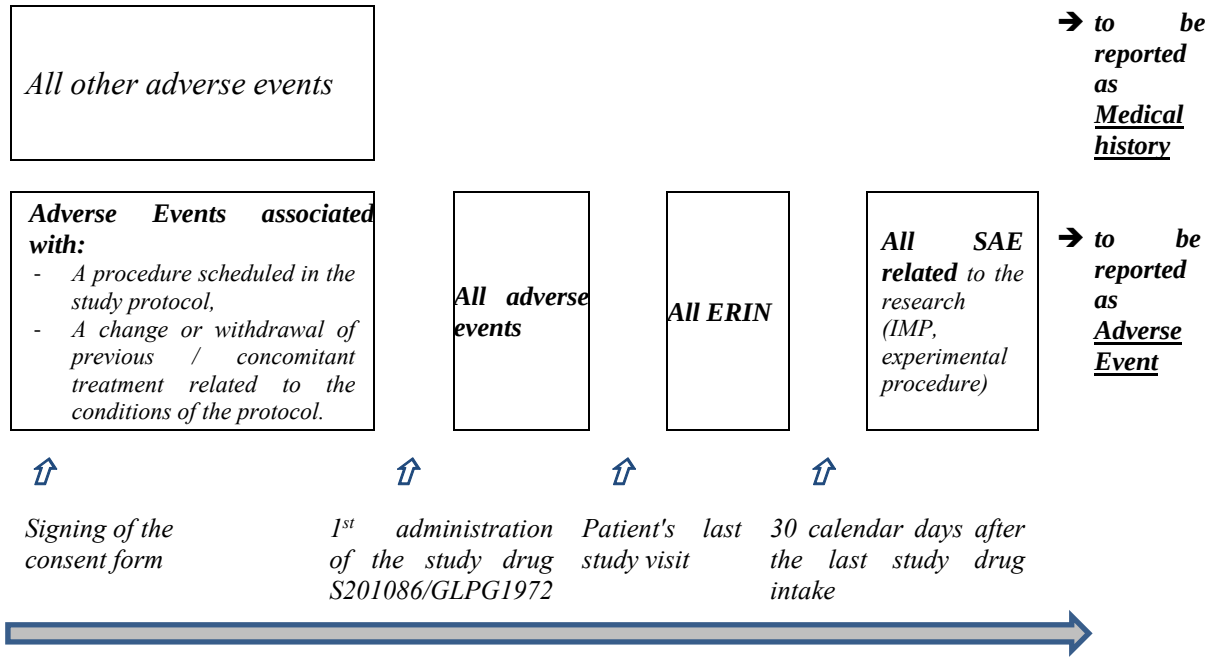
8.9. Reporting procedures

8.9.1. Time frame for adverse event reporting

Any event meeting the above mentioned definitions (see sections 8.3 to 8.77) must be reported to the sponsor on an AE form if it occurred:

- before the first intake of the study drug, **for event associated with any procedure/condition required by the study protocol**: procedure (Imaging, etc.), change or withdrawal of previous/concomitant treatment relating to the conditions of the protocol.
- at any time after the first intake of the **study drug** up to the patient's last study visit for all events,
- after the patient's last study visit:
    - up to 30 calendar days after the last study drug intake for all ERIN, regardless of the supposed role of the research (IMP or experimental procedure).
    - irrespective of the time of onset after the end of the study in case of serious adverse event related to the research (IMP or experimental procedure).

Of note, events occurring between the signature of the informed consent and the first administration of the study drug for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as **medical history** in the dedicated form of the e-CRF.



8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the patient's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the patient or a third person, …) and any other relevant information which he/she has learned of the event,
- **Assess** the event in terms of seriousness, severity and causality,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately),
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfill his/her regulatory obligations** to the Regulatory Agencies and/or to the IRB/IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Regulatory Agencies in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis, or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, severity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must documented in the "Adverse event" page previously created for the event (e-CRF).

If the adverse event has not resolved at the patient's final visit in the study, the patient must be followed up suitably and any information on the outcome of the event will be noted on the « Adverse Event » page previously created for the event (e-CRF). The information will be recorded at a follow-up visit.

If the follow-up of the patient is not done by the investigator him/herself (hospitalization, followed by a specialist or the patient's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the patient.

8.9.2.3. Recording Methods in the e-CRF

Adverse events must be documented on the AE page of the e-CRF.

In case of chronic disease:

- if the disease is known when the patient enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the «Adverse Event» page previously created for the event (e-CRF) which will clearly describe the diagnosis.

8.9.2.4. Procedure for an event requiring an immediate notification (ERIN)

Any ERIN (SAE, pregnancy and other special situation) must be reported within 24h of knowledge.

8.9.2.4.1. Serious Adverse Event

In case of Serious Adverse Event (SAE), the investigator must:

- **Immediately** after being informed of this event, **fill in** the **patient's medical file** as well as the **«Adverse Event» page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into Inform, an e-mail will be immediately and automatically sent to the sponsor.
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Regulatory Agencies and/or to the IRB/IEC, in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes serious (ERIN), this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately send them by fax (or e-mail) to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line is +33.1.55.72.60.00.
- As soon as the e-CRF becomes available, the investigator should enter these data in the «Adverse Event» page of the e-CRF.

8.9.2.4.2. Special situations

- In case of a special situation, the investigator should report it on a "special situation" page of the e-CRF. Any AE associated with a special situation should also be capture in the eCRF (**«Adverse Event»** page).

  Any SAE associated with a special situation **must be reported following the SAE procedure.**

  In case the e-CRF is unavailable when the investigator was informed of a special situation, he/she should, within 24 h of knowledge, complete a paper "Special situation" form, send it by fax (or e-mail) to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line is +33.1.55.72.60.00.
  As soon as the e-CRF becomes available, the investigator should enter these data in the «Special situation» page of the e-CRF.

- If a special situation concerns a person around the study participant, the investigator should not report this on eCRF but must fill in the paper-based "Special Situations Report form" and send it within 24 h of knowledge by fax (or e-mail) to:
  SGS Life Science Services Medical Affairs (LSS MA) Department (Fax #: +32 15 299 394 or e-mail: be.life.saefax-ma@sgs.com).

8.9.2.4.3. Pregnancy

If pregnancy concerns a patient or a partner of a patient, the investigator immediately after being informed of this event **must fill in the paper-based "Pregnancy Report form"** and send it within 24 h of knowledge by fax (or e-mail) to:

SGS Life Science Services Medical Affairs (LSS MA) Department (Fax #: +32 15 299 394 or e-mail: be.life.saefax-ma@sgs.com).

The outcome of pregnancies must be reported. A follow-up contact should be scheduled at the expected time of delivery.

8.9.3. Responsibilities of the sponsor

In accordance with international guidelines, the assessment of the seriousness and the causality of AE are usually made by the investigator but falls also under sponsor's duties. The causality and the seriousness may be upgraded (but never downgraded) by the sponsor. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

The sponsor is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Regulatory Agencies and Ethics Committees.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Safety Information section of Investigator's Brochure.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data to the appropriate Authorities and to all the investigators involved, according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations.

The concerned Authorities will be notified as soon as possible by the sponsor of the DSMB recommendations if any, where relevant for the safety of patients (*i.e.* modification or termination of the study).

8.10. Responsibilities of data safety monitoring board

In accordance with the DSMB charter and the rules for DSMB functioning (refer to section 12.4 of the clinical study protocol), the DSMB is responsible for reviewing the safety data on a regular basis, and providing written recommendations to the Sponsor regarding the conduct of the study (modification or termination).

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Pharmacokinetics

S201086/GLPG1972 concentration (and metabolite[s] if applicable) will be analyzed. Plasma analyses for S201086/GLPG1972 will be performed by the assay centre using a validated analytical method.

For all patients, blood samples (5 mL/time-point) will be collected in W004, W012, W028, W040, W052 and if applicable at the withdrawal visit (WD) to determine S201086/GLPG1972 (and metabolite[s] if applicable) plasma concentrations:

- At W004, W012, W052 visits and if applicable at the withdrawal visit (WD), one (1) time-point will be collected (pre-morning dose PK sample). At these visits, the patient takes the IMP at the site.
- At W028 visit, a pre dose and a post dose sample will be collected. The pre dose sample is taken at the site. Thereafter the patient takes the IMP at the site. The post dose sample is taken 2-4 hours after IMP intake.
- At W040 visit, a post dose sample will be collected. The post dose sample is taken 4-8 hours after IMP intake. This visit is likely to be scheduled in the afternoon. Patients take their IMP at least 4 h before sampling and report the time of dosing to the study staff.

It is also important that for days at which a PK-sample is taken, patients document/report the time of dosing on the previous day (or estimation).

The sampling conditions and handling details will be described in a specific technical document that will be available in time before the center initiation visit.

9.2. Biomarkers

9.2.1. Biochemical biomarkers

In order to improve the knowledge of the study drug, assessment of:

- ARGS biomarker,
- Other cartilage (uCTX-II) and bone (sCTX-I, uCTXIα) degradation markers will be performed.

ARGS is biomarker of ADAMTS-5 activity.

In case of consent withdrawal, related samples will be destroyed after mandatory assessment is completed (6 months after consent withdrawal).

9.2.2. Genomic Biomarkers (optional)

Patients in the CL2-201086-002/GLPG1972-CL-201 study will be requested to undergo optional investigations on a voluntary basis. All patients will have to sign specific informed consent forms. The consent given to these analyses can be withdrawn at any moment without compromising the participation in the overall clinical study investigations. In addition, in case of consent withdrawal, related samples will be destroyed before any optional analysis is completed.

The aim of this optional investigation is to search for evidence of an association between potential genomic biomarkers, the investigated disease and/or the treatment response.

Samples from all patients will be collected in order to extract DNA and RNA and analyze genomic biomarkers (variations of DNA and RNA characteristics).

Overall results of the genomic biomarkers assessment may be transmitted to the patient upon his/her request at the end of the study.

There will be no communication of individual results neither to the investigator nor to the patient.

9.2.3. Biomarkers assessment

- ARGS will be measured in serum at W000, W004, W012, W028, W052, and WEND (and in case of premature withdrawal).
- Assessment of cartilage and bone degradation markers will be performed at W000, W004, W012, W028, W052, and WEND (and in case of premature withdrawal).
- Genomic assessment will be performed at W000 and W052 (optional).

The sampling conditions and handling details will be described in a specific technical document including the description of the methods used for measurement that will be available in time before the center initiation visit. The results of these exploratory biomarkers will be reported separately.

9.2.4. Sampling and storage

Sampling and storage conditions are shown in the table below:

Biomarkers assessed	Experimental conditions		
	Sampling*	**Matrix**	**Storage**
ARGS	10mL	Blood (serum)	-80°C
Cartilage (uCTX-II) and bone (sCTX-I, uCTXIα) +	10mL	Blood (serum)	-80°C
	10mL	Blood (plasma)	-80°C
	20mL	Urine	-80°C
optional+			
DNA(W000)	10mL	Blood	-80°C
RNA(W000)	10mL	Blood	-80°C
(W052)	10mL		

**includes also back up and additional samples that will be stored to measure today unknown biomarkers that may appear in the literature in the coming years.*

+ This list could be updated according to markers that may appear in the literature in the coming years.

The actual sampling times must be recorded in the eCRF.

9.2.5. Labeling and shipping to analytical centre

Labeling and shipping to analytical center will be described in a specific document (lab manual).

9.2.6. Transfer of analytical results

Final analytical results will be transferred to Data Management according to section 14.3.

All samples will be destroyed within a maximum of 25 years after the end of the study or earlier if requested according to local legislation. If the maximal storage duration is specified by each patient at the time of his/her informed consent, samples will not be stored.

The samples may be used after the end of the study for other biomarker assessments unknown today but that may appear in the literature in the coming years.

The genomic samples may be used after the end of the study for other genomic assessments in relation to the study drug or the disease (OA) not specified in the protocol in light of new scientific knowledge or technology, but will not be used for the elaboration of a DNA bank.

9.3. Other

Not Applicable.

10. STATISTICS

10.1. Statistical analysis

The Statistical Analysis Plan and associated templates for Tables, Listings and Graphs, will be written just after finalizing the protocol and definitively completed before breaking the blind of the study These specifications will detail the implementation of all the planned statistical analyses in accordance with the main characteristics stated in the protocol.

10.1.1. Endpoints

10.1.1.1. Efficacy endpoints

10.1.1.1.1. Primary efficacy endpoint

The primary efficacy endpoint is the **change from baseline to W052 in cartilage thickness in the cMTFC** assessed by qMRI on the target knee (centralized reading).

10.1.1.1.2. Secondary efficacy endpoints

The secondary efficacy endpoints are:

- **The proportion of "Structural progressors" at W052**. A "structural progressors" is defined as a patient who had an 8% cartilage loss in cMTFC between baseline and W052.
- **The change from baseline to W052 in WOMAC subscales scores for pain, function and stiffness**.
- **The change from baseline to W052 in pain in the target knee** measured with a 100-mm VAS.
- **The change from baseline to W052 in patient global assessment** of disease activity measured with 100-mm VAS.
- **The proportion of OMERACT-OARSI responders at W052.** A responder is defined according to WOMAC and PGA as a patient who had a high improvement in pain or in function ≥ 50% and absolute change ≥ 20 or, improvement in at least 2 of the 3 following:
  - Pain ≥ 20% and absolute change ≥ 10
  - Function ≥ 20% and absolute change ≥ 10
  - Patient's global assessment ≥ 20% and absolute change ≥ 10.
- **The change from baseline to W052 in cartilage thickness of the total tibiofemoral compartment** of the target knee using qMRI (centralized reading).
- **The change from baseline to W028 and to W052 in bone area of the medial femoral condyle surface** of the target knee using qMRI (centralized reading).
- **The change from baseline to W052 in JSW** of the target knee measured by x-ray (centralized reading).
- **Pain: Analgesic consumption:** at every visit up to W052

10.1.1.2. Safety endpoints

The safety endpoints are:

- For AEs:
  - The number of AEs, the number and percentage of patients reporting at least one AE.

The AE are:

Serious adverse events (SAE) during the study, according to the investigator or sponsor opinion.
Emergent adverse event (EAE) under treatment. The definition of EAE will be provided in the Statistical Analysis Plan.

- For clinical laboratory evaluation:
  - The value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as the change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.
  - The number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for PCSA values for discrete parameters, except for urinary parameters.

The clinical laboratory evaluations are biochemistry, haematology and urinary parameters.

- For vital signs and clinical examination:
  - The value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as the change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.
  - The number of emergent relevant decreases/increases, number and percentage of patients with at least one emergent relevant decrease/increase.

The vital signs and clinical examination parameters are the body weight (kg), BMI (kg/m²), supine SBP (mmHg), supine DBP (mmHg) and supine pulse rate (bpm).

- For ECG parameters:
  - The value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as, for continuous parameters the change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.

The electrocardiogram parameters are, the presence of clinically significant ECG abnormalities (yes/no), the heart rate (bpm), the QRS duration (msec), the PR interval (msec), the QT interval (msec), the QTcF – Fridericia's correction formula interval and the RR interval (msec).
Moreover, other endpoints will be derived from the QTcF – Fridericia's correction formula interval's electrocardiogram parameter: the values and changes from baseline in classes, considering threshold defined in ICH E14 (i.e., ≤ 450,]450; 480];]480; 500] and > 500 ms for values, and ≤ 30,]30; 60] and > 60 ms for changes).

10.1.1.3. Biomarkers endpoints

The biomarker endpoints (exploratory) are:

- For drug activity:
  - The change from baseline to each post baseline (W004, W012, W028, and W052) visits in ARGS concentration (serum).
  - The value at baseline and at each post baseline (W004, W012, W028 and W052) visits in ARGS concentration (serum).
- For cartilage degradation (bone degradation respectively), uCTX-II (sCTX-I and uCTXIα respectively):

- The change from baseline to each post baseline visit (W004, W012, W028, and W052).

- The value at baseline and at each post baseline visit(W004, W012, W028, and W052)

10.1.1.4. Other endpoints

Not applicable.

10.1.1.5. Pharmacokinetics endpoints

Plasma concentrations of S201086/GLPG1972 (and those of metabolite[s] if applicable) will be documented with descriptive statistics (mean, median, standard deviation, minimum and maximum) at each time-point and each dose for trough plasma concentration (C_{trough}) values.

S201086/GLPG1972 (and metabolite[s] if applicable) plasma concentration measurement will be used in order to build a population pharmacokinetics model. This analysis will provide pharmacokinetic parameters and their associated variability. The influence of covariates will be investigated. The pharmacokinetic analysis will be the object of separate data analysis plan (DAP) and report.

Exploratory assessment of the relationship between exposure and pharmacodynamics (as safety and efficacy) will be performed and if applicable, population pharmacokinetic-pharmacodynamic models will be developed and a DAP will be set up and reported separately.

10.1.2. Analysis sets and subgroups / Treatment groups

10.1.2.1. Analysis sets and subgroups

- **Randomised Set (RS):**
  All patients to whom a therapeutic unit was randomly assigned using IWRS.
- **Safety Set (SS):**
  All patients having taken at least one dose of IMP.

No formal subgroup analysis is planned for this study.

10.1.2.2. Treatment groups

Treatment groups considered will be S201086/GLPG1972 75 mg, S201086/GLPG1972 150 mg, S201086/GLPG1972 300 mg and placebo.
Analyses performed on the RS and on the SS will be based on the treatment group assigned as per randomization (randomized treatment).

10.1.3. Statistical methods

10.1.3.1. General considerations

10.1.3.1.1. Multiplicity issues

In order to take into account the multiplicity of comparisons associated with the primary objective of the study (demonstration of superiority of at least one S201086/GLPG1972 dose as compared to placebo on the primary efficacy endpoint); a Dunnett's procedure will be used for the primary analysis. More details on the strategy defined for handling multiplicity issues are provided in Section 10.1.3.3.

For secondary endpoints, the same strategy as the one use for primary analysis will be used for handling multiplicity issues for doses comparison and no adjustment to control the type I error for multiple endpoints will be used.

10.1.3.1.2. Handling of missing data

For the primary analysis, a mixed-effects model for repeated measures approach will be used. For patients with an early discontinuation to the study (delay between the Early Termination and baseline less than 2 months) and without any post baseline measurement of the primary endpoint, a multiple imputation procedure will be used to impute the missing evaluations, assuming that those patients would be in their randomized arm. This approach allows considering that patients will keep the benefit of the randomized treatment after study discontinuation. Multiple imputation, pattern mixture model placebo based imputation, tipping point method and observed cases will be considered for sensitivity analyses (Mallinckrodt & al., 2013).
More details on the strategy defined for handling missing data are provided in Section 10.1.3.3.

10.1.3.1.3. Statistical elements

10.1.3.1.3.1. Descriptive statistics

The following descriptive statistics will be provided depending on the nature of considered data:

- **Discrete data**: number of observed values, number and percentage of patients per class.
- **Continuous data**: number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.

10.1.3.1.3.2. Estimations and statistical tests

The type I error of the statistical tests will be set at 5% (two-sided situation), which is consistent with the objective of demonstrating the superiority of S201086/GLPG1972 versus placebo (one-sided situation at 2.5%).

The treatment effect will be estimated as well as its accuracy: estimate of the difference, standard error of the estimate and two-sided 95% confidence interval of the estimate.

When formal comparison between treatment groups is performed, the two-sided p-value associated with the treatment effect will also be provided.

10.1.3.2. Study patients: Disposition, baseline characteristics and follow-up

Demographic data and other baseline characteristics such as prognostic factors and baseline value of endpoints will be described by treatment group, to assess their comparability, by treatment group and with the overall in the RS.

Disposition of patients, including reasons for withdrawal, protocol deviations, extent of exposure and treatment compliance, as well as concomitant treatments will be described in the RS. Extent of exposure and treatment compliance will also be described in the SS.

The time to patient discontinuation and to premature IMP withdrawal will be described in the RS, using a Kaplan-Meier analysis in order to assess the drop-out pattern between the treatment groups; as well as withdrawn and completed patients' characteristics in the RS.

10.1.3.3. Efficacy analysis

10.1.3.3.1. Primary efficacy endpoint

10.1.3.3.1.1. Primary analysis

Main analysis strategy:
In order to meet the primary objective of the study, the efficacy of at least one dose of S201086/GLPG1972 as compared to placebo after 52 weeks of treatment in reducing cartilage loss in patients with knee OA will be assessed from the change from baseline to W052 in cartilage thickness as measured in the medial central tibiofemoral compartment on the target knee, in patients of the RS. A restricted maximum likelihood (REML)-based, mixed-effects model for repeated measures approach (so called Mixed-effects Model for Repeated Measures – MMRM) using all longitudinal observations at each post-baseline visit will be used (main analysis). The MMRM as a primary analysis will assume that patients would keep the benefit of the randomized treatment after study discontinuation. For patients with an early discontinuation to the study (delay between the Early Termination and baseline less than 2 months) and without any post baseline measurement of the primary endpoint, a multiple imputation procedure will be used to impute the missing evaluations, assuming that those patients would be in their randomized arm. For patients with a discontinuation after 2 months since the last qMRI, but before the next planned visit, the qMRI will be associated with the next planned visit. Other missing evaluations will be handled by the direct likelihood approach through the MMRM modeling. The treatment comparisons associated with the primary analysis will be the contrasts between each dose of S201086 and placebo at the change from baseline to W52. Analysis will include the fixed, categorical effects of treatment, regions (Asia and Rest of the World), time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline, time-by-baseline interaction.

The analysis will fit an unstructured covariance matrix, and the assumptions underlying the model will be checked.

The consistency of the results between the Asian-region population and the non-Asian-region population will be evaluated on primary endpoint, according to the Method 2 defined in Ministry of Health Labor and Welfare Notification (MHLW) Notification "Basic principles on Global Clinical Trials". Treatment effect estimates and confidence intervals will be provided, for each dose, in Asian-region population and non-Asian-region population. In case of a statistically significant overall treatment effect (in favor of S201086/GLPG1972) at a

considered dose, the results will be considered consistent if the observed treatment effects in Asian-region and non-Asian-region patients are in favor of S201086/GLPG1972.

Sensitivity analyses:
To assess the robustness of the analysis results towards the method of handling missing data, a similar procedure will be repeated according to the following variations:

- considering the multiple imputation method for all missing values,
- considering analysis is restricted to patients of the RS having a non-missing value at W52 for the primary endpoint,
- considering the pattern mixture model, placebo based imputation for each missing data (including patients with an early discontinuation and without any post baseline value for the primary endpoint),
- considering the tipping point method for all missing values,

using a single three-way analysis of covariance (ANCOVA) model with treatment and regions as fixed, categorical effects, as well as baseline as continuous fixed covariate. The assumptions underlying the model will be checked.

10.1.3.3.1.2. Secondary analyses

The existence of a dose-response relationship according to the change from baseline to W052 in cartilage thickness in the central medial tibiofemoral compartment will be checked using the MCP-Mod.

Overall similarity of the dose-response relationship in the entire population, Asian population and non-Asian population will be performed through graphical visual inspection on the primary endpoint, in patients of the RS.

For each treatment group, descriptive statistics will be provided for the primary endpoint (in terms of value at each visit and change from baseline to each post-baseline visit), overall and by regions.

10.1.3.3.2. Secondary efficacy endpoints

For the proportion of "structural progressors" and proportion of OMERACT-OARSI responders at W052, the difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS, considering a multiple imputation for handling all missing data and using a logistic model, including the fixed, categorical effects of treatment, regions (Asia and Rest of the World), as well as the continuous, fixed covariates of baseline.

The difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS, on continuous secondary efficacy endpoints at W052, with the same strategy as the main analysis of the primary endpoint: multiple imputation for patients without any post-baseline value followed by a MMRM using all the longitudinal observations at each post-baseline visit. Analysis will include the fixed, categorical effects of treatment, regions (Asia Rest of the World), visit and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline, visit-by-baseline interaction.

For the change from baseline to W052 in JSW and the change from baseline to W028 in bone area, the difference between each S201086/GLPG1972 dose and placebo will be studied in patients of the RS at W052 (respectively W028), considering a multiple imputation method for

handling all missing data at W052 (respectively W028), and using an ANCOVA. Analysis will include the fixed, categorical effects of treatment, regions (Asia, US and Rest of the World), as well as the continuous, fixed covariate of baseline.

For analgesic consumption, number and percentage of patients by treatment reported will be provided, overall and by treatment group.

For each treatment group, descriptive statistics will be provided for all secondary endpoints (in terms of value at each visit and change from baseline to each post-baseline visit for continuous endpoint), overall and by regions.

10.1.3.4. Safety analysis

10.1.3.4.1. Adverse events

Number of events, number and percentage of patients reporting at least one event, presented by system organ class and preferred term (depending on the analysis), will be provided for SAEs and EAEs over the study.

EAEs will be described according to the seriousness, the intensity, the relationship, the action taken regarding the IMP, the requirement of added therapy, the outcome and the time to onset.

Of note, the seriousness and the relationship to the IMP of the adverse event correspond to the investigator opinion or, in case of events upgraded by the sponsor for seriousness or for causality in case of SAE, to the sponsor opinion.

10.1.3.4.2. Clinical laboratory evaluation

The following analyses will be performed, depending on the nature of considered endpoints (*i.e.,* quantitative or qualitative):

- Descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and, if applicable, on change from baseline to last post-baseline value under treatment.
- Number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for PCSA values.
- Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and cut-offs, and using shift tables from baseline to the worst (high and/or low) values under treatment.

10.1.3.4.3. Vital signs, clinical examination and other observations related to safety

10.1.3.4.3.1. Vital signs and clinical examination

Supine blood pressure, body weight and BMI will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.

Number of emergent relevant decreases/increases, number and percentage of patients with at least one emergent relevant decrease/increase, based on Supine SBP, Supine DBP and weight will be provided.

10.1.3.4.3.2. Electrocardiogram

ECG parameters will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as, for quantitative endpoints, in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment. Moreover values and changes form baseline of corrected QT interval will be described in classes, considering thresholds defined in ICH E14 (i.e., ≤ 450,]450; 480],]480; 500] and > 500 ms for values, and ≤ 30,]30; 60] and > 60 ms for changes).

ECG abnormalities will be described.

10.1.3.5. Biomarkers analysis

For each patient longitudinal evolution of biomarker will be studied through graphical displays.

The association between biomarker endpoints and change from baseline on cMTFC at W052 will be studied.

For each treatment group, descriptive statistics will be provided for all biomarker endpoints, overall and by region.

10.1.4. Interim analysis

Not applicable

10.2. Determination of sample size

The determination of the sample size was performed considering the change from baseline to W052 in cartilage thickness in the cMTFC, expressed in mm and measured by qMRI.

The objective is to demonstrate that at least one S201086/GLPG1972 dose is superior to placebo in the RS, based on a two-sided Dunnett test for multiple comparisons. The Dunnett test is used in order to maintain the experiment wise type I error at 5% (two-sided setting).

Two hundred and thirteen (213) patients per treatment group will provide a minimal power of approximately 70% to conclude for at least one dose that S201086/GLPG1972 is superior to placebo if the true difference is 0.0825 mm for at least one dose, assuming a standard deviation of 0.30 mm (Lohmander et al., 2014).

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Regulatory Agencies to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the structure mentioned in a separate document (section 1).
- Details of clinical site monitoring are documented in a clinical monitoring plan (CMP) or similar document. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the applicable protocol requirements.

Training sessions may be organized for the investigators and/or instruction manuals may be given to the investigators.

12.1.2. During the study

The investigator will allow the monitor to:

- review of the study site's processes and procedures,
- verify appropriate clinical investigator supervision of study site staff and third party vendors,
- inspect the site, the facilities and the material used for the study,
- meet all members of his/her team involved in the study,
- consult the documents relevant to the study,
- have access to the electronic case report forms (*i.e.* access to an analogic phone line or his/her computer) and/or to the e-PRO service provider's database,
- check that the electronic case report forms/e-PRO have been filled out correctly,
- directly access source documents for comparison of data therein with the data in the electronic case report forms and/or to the e-PRO service provider's database,
- verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerized medical file

If computerized medical files are used the following requirements apply.

The computerized medical file must:

- Be validated to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records
- Have the ability to generate accurate and complete copies of records
- Be ready retrievable and accurate throughout the records retention period
- Make use of secure, computer-generated, time-stamped audit trails
- Be accessible by the study monitor

If the computerized medical files do not fulfil these requirements the computerized medical files including updates or changes need to be printed, numbered, signed, and dated. All printed medical files (and changes therein) should be made available to the monitor during each site visit.

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Regulatory Agencies may also carry out an inspection in the facilities of the sponsor and/or the study centers. The sponsor will inform the investigators concerned immediately upon notification of a pending study centers inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Regulatory Agencies and persons responsible for the audit:
- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all of the documents relevant to the study.

If the computerized medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the patients and, if the computer system used allows, the record of the changes made during the study.

If the computerized medical file is considered as validated, the investigator undertakes to:
- give access to the representatives of the Regulatory Agencies and persons responsible for the audit to the computerized medical files of all patients,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory committees

DSMB recommendations will be forwarded to the IRB/IEC/ Regulatory Agencies only if relevant for the safety of patients.
According to the "Guideline on data monitoring committees" (Guideline CHMP/EWP/5872/03 Corr., 27 July 2005) and "Establishment and Operation of Clinical Trial Data Monitoring Committees" (FDA guidance, March 2006), the decision to set up of a DSMB should take into account the study population as well as the study duration. The present study takes place in patients aged between 40 and 75 years with knee osteoarthritis. As this vulnerable population (include aged patients) will be exposed to study treatment for up to 52-weeks, the set-up of a DSMB is justified in order to detect any potential harm to patients as early as possible.

All along the study, in order to ensure patients' safety, the DSMB will be responsible for a follow up of the patients by a periodical review of patients' data, especially adverse events. The DSMB will be provided with the information on study treatment by the authorized person of the Servier's Clinical Supplies Unit. The DSMB will treat all data as strictly confidential and will not disclose them to anyone else than members of the DSMB.

Details of the role and organization of the DSMB are detailed in a separate DSMB charter.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Patient information and consent form" document, the list of investigators document, the insurance documents, the Investigator's Brochure of administered IMPs will be submitted to (an) IRB(s)/IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964 (see Appendix 1) with the GCP and with the applicable regulatory requirements.

13.3. Patient information and informed consent

In any case, the patient (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator (or designee) is to collect written consent from each patient before his/her participation in the study. Prior to this, the investigator (or designee) must inform each patient of the objectives, benefits, risks, and requirements imposed by the study, as well as the nature of the IMPs.

The patient will be provided with an informed consent form in clear, simple language. He/she must be allowed ample time to inquire about the details of the study and to decide whether or not he/she wishes to participate.

Two original informed consent forms must be completed, dated, and signed by the patient and the investigator (or designee).

If the patient is unable to read, an impartial witness should be present during the entire informed consent collection process. The patient must give consent orally and, if capable of doing so, complete, sign, and personally date the informed consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The patient will be given one signed original informed consent form, the second original will be kept by the investigator.

Note that each patient's privacy is protected under the Health Insurance Portability and Accountability Act (HIPAA) privacy and security rules (for US only). The privacy rule requires appropriate safeguards to protect the privacy of personal health information, and sets limits and conditions on the uses and disclosures that may be made of such information without patient authorization. The rule also gives patients the rights over their health information, including rights to examine and obtain a copy of their health records, and to request corrections. The

security rule requires appropriate administrative, physical and technical safeguards to ensure the confidentiality, integrity, and security of electronic protected health information.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Regulatory Agencies.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Patient Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required eliminating an immediate risk to the study patients.

Each patient affected by the amendment or an independent witness must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Source data

Source data and source documents of the center should be clearly identified in a specific, detailed and signed document before the beginning of the study.

The following documents are considered as source documents:

- Notes in the medical file (including nurse files)
- Therapeutic Unit Tracking Form (TUTF)
- Report/images (*e.g.* laboratory, ECG, MRI, X-Ray, etc.)
- VAS (pain) and VAS (PGA) recorded by e-PRO
- Requisition form (*e.g.* PK)

14.2. Study data

A 21 CFR Part 11-compliant electronic data capture system is going to be used for this study. An electronic case report form (eCRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the patient's Medical File.

Upon entry, data will be transmitted via the Internet from the study center to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each patient visit, and all other documents provided by the sponsor (*e.g.* documents relating to the IMP management…).
Data recorded directly on eCRF and considered as source data (see section 14.1) must be collected immediately in the eCRF. The other eCRF forms must be completed as soon as possible following each visit.

All corrections of data on the eCRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Inform software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorized personnel only, whether resident within the investigator's sites, the sponsor or third parties.
Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However the investigator has the possibility to modify a data if deemed via a request to the sponsor.

After the last visit of the patient, the investigator or co-investigator must attest the authenticity of the data collected in the eCRF by entering his/her user name and password.

After the data base lock, the investigator will receive a CD-ROM containing patient data of his/her center for the study file.

14.3. Data management

Data are collected via an eCRF and stored in a secured database.

For data collected on the e-CRF, the Data & Clinical Logistics of I.R.I.S. is responsible for data processing, including data validation according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

The Data & Clinical Logistics Division of I.R.I.S. is responsible for all data transfers.

The following CROs: MRI central reading center, X-ray central reading center, ePRO provider, ECG central reading center, central laboratory for laboratory tests, central laboratory for bioanalytical data, central laboratory for biomarkers analysis, CRO IWRS provide electronic transfer of computerized data to the clinical studies data management department. Data are transferred according to a transfer protocol issued by the I.R.I.S. clinical studies data manager.

ARGS and other cartilage and bone biomarkers and PK data will be transferred to the Data & Clinical Logistics Division of I.R.I.S. after clinical database lock.

The Medical Data Department of I.R.I.S. is responsible for data coding including:
- medical / surgical history, AEs and procedures using the Medical Dictionary for Regulatory Activities (MedDRA),
- medications using the World Health Organization, Drug Dictionary (WHO-DRUG).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

When data validation is achieved, a blind review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked and the IMP codes will be unblinded and made available for data analysis.

14.4. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation, or for US sites two years after approval of the New Drug Application (NDA) or discontinuation of the Investigational New Drug (IND) (it include all source data, and that these data should be readable during the archiving period).

At the end of the study, the investigator will be provided with a copy of each patient's data on a CD-ROM support. These data include all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

15. INSURANCE

15.1. For non US countries:

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' approval of which is required.

15.2. For US country only:

15.2.1. Indemnification

Under the conditions of a contract concluded between investigator, site and the sponsor Galapagos NV or designee, which shall prevail, the sponsor Galapagos NV shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the clinical study protocol (CSP), Galapagos NV's instructions and applicable local regulations.

The investigator must notify the sponsor Galapagos NV immediately upon notice of any claims or lawsuits.

15.2.2. Insurance

The sponsor Galapagos NV shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Save in case of gross negligence or willful misconduct of the investigator, and provided that the patient has been treated according to the CSP and Galapagos NV's instructions, any injury caused to a patient which is the direct result of his/her participation to the clinical study shall be covered by Galapagos NV's insurance.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

Les Laboratoires Servier and Institut de Recherches Servier and Galapagos ("**Servier**"), and I.R.I.S. affiliate, and Galapagos N.V. ("**Galapagos**") entered into a Product Development, Option, License and Commercialization Agreement dated as of 28 June 2010 (as amended from time to time, the "**Servier-Galapagos Agreement**"), which outlines their rights and responsibilities relating to ownership of the results of the Study, data sharing and publications.

As required by the Servier-Galapagos Agreement, each of I.R.I.S. and Galapagos will ensure in their respective territory that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any draft of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to I.R.I.S. and Galapagos. As between I.R.I.S. and Galapagos, each of them shall ensure that the other has the opportunity to review any proposed publication and/or communication in accordance with Article 6 of the Servier-Galapagos Agreement.

The investigator, who submitted the draft, shall take the comments received from either co-sponsor into due consideration.

As the study is a multicenter one, the first publication must be performed only with data collected from several centers and analyzed under the responsibility of I.R.I.S for the ROW Territories and Galapagos for US Territory. The investigator commits himself not to publishing or communicating data collected in only one center or part of the centers before the publication of the complete results of the study, unless prior written agreement from the other investigators, I.R.I.S. and Galapagos has been provided.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the patient, the investigator will inform the patient's general practitioner about his/her patient's participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the coordinators and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favorable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study patients.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Regulatory Agencies in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by I.R.I.S. in compliance with I.R.I.S. standard operating procedure and Galapagos requirements.

The sponsors' representatives and the coordinators must mutually agree on the final version. One copy of the final report must be dated and signed by the coordinators and the sponsor's representatives.

17.2. Concerning the sponsor

The sponsor undertakes to:

- supply the investigator with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study,
- supply the investigator with investigator's brochure if the study drug is not marketed,

- obtain any authorization to perform the study and/or import license for the IMP administered that may be required by the local authorities before the beginning of the study,
- provide coordinators annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to S201086/GLPG1972 and study CL2-201086-002/GLPG1972-CL-201 are strictly confidential. The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer, and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.
He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study patients. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorization of the sponsor.

The investigator must not disclose any information without the prior written consent from the sponsor, except to the representatives of the Regulatory Agencies, and only at their request. In the latter case, the investigator commits himself/herself to informing the sponsor prior to disclosure of information to these authorities.

A patient screening log and a full identification and enrolment list of each patient will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Regulatory Agencies. The information will be treated in compliance with professional secrecy.

The patient screening log must be completed from the moment the investigator checks that a patient could potentially take part in the study (by assessment of patient medical history during a visit or by examination of the medical file).

17.3.2. Organization of the center

The Investigator can delegate study tasks under his/her responsibility to others. Tasks can only be delegated to persons that are qualified to perform that specific task. An “Organization of center” or similar document needs to be completed for documentation purposes.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the center.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- to provide his/her dated and signed English curriculum vitae (CV) or to complete in English the CV form provided by the sponsor or representative and to send it to the sponsor, together with that of his/her co-investigator(s),
- to provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- to provide any other document required by local regulation (e.g. Food & Drug Administration 1572 form),
- to send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the patients' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

18. REFERENCES

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven

interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

Appendix 3: Knee Pain Visual Analog Scale

KNEE PAIN (Screening visit)

"How would you rate the pain you have felt in each knee within the last 48 hours?"

Please indicate on the line the place that best expresses your pain as you feel it within the last 48 hours.
0= no pain (on the left) and 100= extreme pain (on the right)

Left Knee:

No pain **Extreme pain**

Right knee:

No pain **Extreme pain**

****

KNEE PAIN (other visits)

"How would you rate the pain you have felt in the study knee within the last 48 hours? If you are unsure which knee is your study knee, please ask your research doctor before answering."

Please indicate on the line the place that best expresses your pain as you feel it within the last 48 hours.
0= no pain (on the left) and 100= extreme pain (on the right)

No pain **Extreme pain**

Appendix 4: Patient Global Assessment of disease activity Visual Analog Scale

PATIENT GLOBAL ASSESSMENT

"Considering all the ways in which your knee osteoarthritis affects you, please rate on this 100 mm scale how well you are doing today"

Please indicate on the line the place that best expresses your feeling as you feel it right now.
0= very well (on the left) and 100=very poorly (on the right)

very poorly **very well**