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.
ROCCELLA 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:

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

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- ✓ 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 zone (Japan, South Korea/Taiwan 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 for male patients and female surgically sterile patients, and 50-75 years for postmenopausal female patients, 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

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

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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 total score and 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)
  - 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.

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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):**
  The Randomised Set (RS) will be constituted of all patients to whom a therapeutic unit was randomly assigned using interactive web response system IWRS. The RS will be used for efficacy analyses. Patients will be analysed according to the randomised treatment.
- **Safety Set (SS):**
  The Safety Set (SS) will be constituted of all patients having taken at least one dose of IMP. The SS will be used for safety analyses. Patients will be analysed according to treatment actually received at inclusion.

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 0.30 mm (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. A missing data Handling will be used for this analysis. 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 W052. Analysis will include the fixed, categorical effects of treatment, regions, 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.

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The consistency of the results between the Asian population and the non-Asian population (respectively between Japanese population and non-Japanese 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 (respectively between Japanese population and non-Japanese 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 (respectively between Japanese population and non-Japanese population) 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 and 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 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.
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.

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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

HENRI DECKX

CLINICAL DEVELOPMENT LEADER: