2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsors:
I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France
GALAPAGOS NV, Generaal de Wittelaan L11 A3, 2800 Mechelen - Belgium</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="2">Test drug
Name of Finished Product:
Not applicable
Name of Active Ingredient:
S201086/GLPG1972</td><td></td></tr>
<tr><td>Individual Study Table Referring to Part of the Dossier</td><td>Volume:</td><td>Page:</td></tr>
<tr><td colspan="3">Title of study:Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis (OA). A 52-week international, multi-regional, multi-centre, randomised, double-blind, placebo-controlled, dose-ranging study
ROCCELLA Study
Protocol No.: CL2-201086-002/GLPG1972-CL-201
European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) No.: No. 2017-004581-10
Universal Trial Number U1111-1205-0321
Clinicaltrial.gov number NCT03595618
The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.</td></tr>
<tr><td colspan="3">Main coordinators:
[redacted]</td></tr>
<tr><td colspan="3">Study countries:
Twelve (12) countries included 932 patients: Argentina (n = 67), Brazil (n = 139), Canada (n = 64), Denmark (n = 74), Hungary (n = 32), Japan (n = 67), Poland (n = 52), Russia (n = 38), South Korea (n = 31), Spain (n = 26), Taiwan (n = 16) and USA (n = 326).</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period:
Initiation date: 14 August 2018 (first visit first patient)
Completion date: 14 July 2020 (last visit last patient)</td><td>Phase of development of the study:
Phase 2</td></tr>
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Objectives:

Primary objective

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.

Secondary objectives:

- 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 of the target knee.
  - Joint space width 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 (PK) 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:

- To assess effect of 3 doses of S201086/GLPG1972 *versus* placebo after 52 weeks of treatment on:
  - Alanine-arginine-glycine-serine 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:

This study was a phase 2, international, multi-regional, multicentre, randomised, double-blind, parallel-group, placebo-controlled, dose-ranging study in patients diagnosed with knee OA.

This study was performed in strict accordance with Good Clinical Practice.

Given the trial failed to meet the primary objective, an abbreviated clinical study report was written.

Number of patients:

Planned: 852 patients in total (213 in each treatment arm).

Included: 932 included* patients (234 patients in the S201086/GLPG1972 75 mg group, 231 in the S201086/GLPG1972 150 mg group, 233 in the S201086/GLPG1972 300 mg group, 234 in the placebo group).

** 6 patients randomised were not included.*

Diagnosis and main criteria for inclusion:

1. Male patients or female patients of non-childbearing potential and not breastfeeding.
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 with 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.

7a. Symptom severity defined by a pain ≥ 40 mm and ≤ 90 mm on a 100 mm VAS at screening and inclusion visits (at screening both knees should be assessed for pain and at least one knee should fulfill pain severity defined on this criterion). A knee not meeting the pain criteria at screening must not be eligible as target knee at inclusion.

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.

9b. 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.

Test drug: S201086/GLPG1972 (tablets)

S201086/GLPG1972 (75 mg, 150 mg or 300 mg) was administered orally once a day with a glass of water preferably in the morning (at the same time) during the treatment period.

Batch numbers: [redacted].

Comparator: Placebo (tablets)

Placebo was administered orally once a day with a glass of water preferably in the morning (at the same time) during the treatment period.

Duration of treatment:

Screening period: up to 5 weeks prior to inclusion visit (W000).

Double-blind treatment period: 52 weeks (from W000 to W052 visit). Eligible patients were 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.

Follow-up period: 2 weeks from W052 or prematurely withdrawn to end of study visit (WEND). Each patient had to have a study end visit 2 weeks after completed or discontinued the study (definitely stopping study treatment), unless the patient withdrew consent.

Criteria for evaluation:

Efficacy measurements:

The change from baseline to W052 in cartilage thickness of the cMTFC of the target knee was assessed using qMRI. The qMRI was performed at inclusion, at W028 and W052 visits, and at the withdrawal visit (WD) if the time window between WD and the previous qMRI (W000 or W028) was ≥ 2 months.

The secondary efficacy criteria were assessed using WOMAC questionnaire, VAS (pain and PGA), X-Ray, qMRI, and by measuring analgesic consumption.

Safety measurements:

The safety criteria were adverse events (grading according to Common terminology criteria for adverse events version 5), laboratory tests (haematology, blood biochemistry, urinary dipstick locally assessed), body weight, vital signs (systolic and diastolic blood pressure, heart rate) and 12-lead electrocardiogram (ECG) parameters.

Pharmacokinetic measurements:

S201086/GLPG1972 concentration was measured in plasma.

Other measurements:

Biochemical biomarkers were measured in blood and/or urine, and genomic biomarkers (optional) were planned.

Statistical methods:

Analysis Sets:

Modified Randomised Set (MRS): all included patients to whom a therapeutic unit was randomly assigned using the Interactive web response system.
Safety Set (SS): all patients having taken at least one dose of investigational medicinal product (IMP).
Biomarker Set: all patients of the MRS having at least one analysable value for cartilage or bone degradation biomarkers criterion.

Study patients (disposition, baseline characteristics and treatments): descriptive statistics were provided in the MRS by treatment group and overall.

Efficacy analysis:

Primary endpoint:

To demonstrate 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, a restricted maximum likelihood-based, mixed-effects model for repeated measures approach using all longitudinal observations at each post-baseline visit (W028) was used on the change from baseline to W052 in cartilage thickness as measured in the cMTFC on the target knee, in patients of the MRS. The analysis included the fixed, categorical effects of treatment, region (Asia and Rest of the World), time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline and time-by-baseline interaction. Several sensitivity analyses were also performed to assess the robustness of the primary analysis results on the handling of missing data and on the management of delayed W052 qMRI assessment due to the coronavirus disease 19 (COVID-19) pandemic.
The estimate of the between group difference (each S201086/GLPG1972 dose minus placebo), associated standard error, two-sided 95% confidence interval and adjusted p-value were provided.
For each treatment group, descriptive statistics were provided for the primary endpoint (in terms of value at each visit and change from baseline to each post-baseline visit), overall and by region, in patients of the MRS.

Safety analysis: descriptive statistics were provided in the SS by treatment group.

Pharmacokinetic analysis: PK analysis is described in the PK report.

Biomarkers analyses: biochemical biomarkers analysis is described in the statistical analysis plan. Genomic biomarkers analysis is not presented in this study report since no genomic analysis was done.

SUMMARY OF RESULTS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Table 1 - Overall disposition of patients and analysis sets

Status		**ALL (N = 932)**
INCLUDED	**n**	**932**
WITHDRAWN DUE TO	**n (%)**	**173 (18.6)**
Adverse event	n (%)	61 (6.5)
Withdrawal by subject	n (%)	50 (5.4)
Other	n (%)	28 (3.0)
Lost to follow-up	n (%)	21 (2.3)
Protocol violation	n (%)	10 (1.1)
Physician decision	n (%)	3 (0.3)
COMPLETED	**n (%)**	**759 (81.4)**

N number of patients overall, n number of patients. Percentages are based on n

Analysis Sets		**S201086/GLPG1972**			**Placebo (N = 234)**	**All (N = 932)**
		75 mg (N = 234)	**150 mg (N = 231)**	**300 mg (N = 233)**		
MRS	n	234	231	233	234	932
SS	n (%)	234 (100)	231 (100)	232 (99.6)	234 (100)	931 (99.9)

% % of the MRS; SS Safety Set

In the MRS, a total of 932 patients were included and randomly assigned to one of the 4 treatment groups in a well-balanced distribution.

BASELINE CHARACTERISTICS

Overall, patients were mostly over 55 years (87.0%) with mean ± Standard Deviation (SD) age of 62.9 ± 7.3 years, 69.3% female and 73.3% White.

All patients were diagnosed with knee OA based on the criteria of the ACR and all patients reported knee pain for at least 6 months and on the majority of days (> 50%) during the preceding month. 99.9% of the included patients had KL radiographic criteria of grade 2 (11.1%) or grade 3 (88.8%). 99.6% of the included patients had grade 1 (32.3%) or 2 (67.3%) OARSI medial tibiofemoral JSN score. Overall, 83.2% of patients had at least one concomitant systemic analgesic treatment at inclusion, 75.3% at least one concomitant NSAID and 9.8% at least one concomitant glucosamine or hyaluronic acid or chondroitin treatment.

This phase 2 study was conducted in patients with knee OA for whom baseline characteristics were in accordance with the target population defined in the study protocol.

At baseline, the mean cartilage thickness in the cMTFC of the target knee in overall patients was 3.25 ± 0.78 mm and this was similar in the treatment groups.

The baseline characteristics were similar between the treatment groups.

EXTENT OF EXPOSURE

In the MRS, the mean ± SD treatment duration was 46.7 ± 13.8 weeks (median was 51.9 weeks) and the mean ± SD treatment compliance was 89.1 ± 14.5% (median was 94.7%) with a similar duration and compliance in the treatment groups. Similar results were observed in the SS.

EFFICACY RESULTS

- **Primary efficacy endpoint: change from baseline to W052 in cartilage thickness of the cMTFC of the target knee**

The primary analysis showed that there was no statistically significant difference between any of the S201086/GLPG1972 groups *i.e.* 75 mg, 150 mg and 300 mg and the placebo group in the change from baseline to W052 in cartilage thickness of the cMTFC. Similar results were observed with the sensitivity analyses for handling of missing data and for delayed W052 qMRI assessment due to the COVID-19 pandemic.

- **Secondary efficacy endpoints**

No statistically significant difference between any of the S201086/GLPG1972 groups and the placebo group was observed for any of the structural and clinical secondary endpoints considered.

SAFETY RESULTS

- **Treatment-emergent adverse events (TEAEs)**

Main results for adverse events in the SS are described in Table 2.

Table 2 - Overall summary for adverse events in the Safety Set

		S201086/GLPG1972			
		75 mg (N = 234)	**150 mg (N = 231)**	**300 mg (N = 232)**	**Placebo (N = 234)**
Patients having reported at least one:					
TEAE	n (%)	174 (74.4)	177 (76.6)	174 (75.0)	174 (74.4)
Treatment-related TEAE	n (%)	36 (15.4)	30 (13.0)	47 (20.3)	37 (15.8)
Severe (*i.e.* CTCAE Grade ≥ 3) TEAE	n (%)	25 (10.7)	27 (11.7)	30 (12.9)	29 (12.4)
Treatment-related severe TEAE	n (%)	1 (0.4)	2 (0.9)	5 (2.2)	2 (0.9)
Serious AE	n (%)	17 (7.3)	17 (7.4)	18 (7.8)	19 (8.1)
Serious TEAE	n (%)	17 (7.3)	17 (7.4)	18 (7.8)	18 (7.7)
Treatment-related serious TEAE	n (%)	0	2 (0.9)	1 (0.4)	2 (0.9)
TEAE leading to treatment withdrawal	n (%)	16 (6.8)	17 (7.4)	20 (8.6)	9 (3.8)
Treatment-related TEAE leading to treatment withdrawal	n (%)	5 (2.1)	8 (3.5)	12 (5.2)	4 (1.7)
Severe TEAE leading to treatment withdrawal	n (%)	5 (2.1)	5 (2.2)	2 (0.9)	3 (1.3)
Treatment-related severe TEAE leading to treatment withdrawal	n (%)	0	1 (0.4)	1 (0.4)	0
Serious TEAE leading to treatment withdrawal	n (%)	8 (3.4)	6 (2.6)	1 (0.4)	5 (2.1)
Treatment-related serious TEAE leading to treatment withdrawal	n (%)	0	1 (0.4)	1 (0.4)	1 (0.4)
Patients who died* during the study	n (%)	0	1 (0.4)	0	0

**fatal TEAE occurring 2 months after last study drug intake.*

In the SS, the percentage of patients with at least one TEAE was similar in each treatment group.

The ***most frequently reported system organ classes (≥ 20% of patients in either treatment group)*** were:

- Musculoskeletal and connective tissue disorders (30.8%, 35.5%, 34.1%, 29.9%, respectively in the S201086/GLPG1972 75 mg, 150 mg, 300 mg groups, and in the placebo group).
- Infections and infestations (37.2%, 34.2%, 30.6%, 36.3%, respectively in each group).

The ***most commonly reported TEAEs*** were:

- Arthralgia (11.5%, 15.2%, 11.2%, 8.1%, respectively in the S201086/GLPG1972 75 mg, 150 mg, 300 mg groups, and in the placebo group).
- Nasopharyngitis (9.0%, 6.9%, 9.5%, 8.5%, respectively, in each group).
- Fall (6.4%, 8.7%, 6.9%, 5.6%, respectively, in each group).
- Gamma glutamyltransferase (GGT) increased (1.3%, 0.9%, 6.9%, 1.7%, respectively, in each group).

The ***most commonly reported severe TEAEs*** were hypertension (0.9%, 2.2%, 2.2%, 2.1%, respectively in the S201086/GLPG1972 75 mg, 150 mg, 300 mg groups, and in the placebo group) and osteoarthritis (0.4%, 2.2%, 1.3%, 0.4%, respectively, in each group).

The frequency of treatment-related TEAEs reported for each PT was low (< 5% of patients) for each treatment group. The ***most frequently reported treatment-related TEAEs*** were:

- GGT increased (0.4%, 0.4%, 4.3%, 1.3%, respectively in the S201086/GLPG1972 75 mg, 150 mg, 30 mg groups, and in the placebo group).
- Alanine aminotransferase (ALT) increased (0.9%, 0.9%, 3.0%, 1.7%, respectively, in each group).
- Aspartate aminotransferase (AST) increased (0.4%, 0.4%, 3.0%, 1.3%, respectively, in each group).
- Headache (3.4%, 1.7%, 2.2%, 1.3%, respectively, in each group).

In the SS, 7.5% of the patients experienced at least one serious TEAE. ***Serious TEAEs*** reported in at least 3 patients in either group were osteoarthritis (0.9%, 0.9%, 1.3%, 0%, respectively in the S201086/GLPG1972 75 mg, 150 mg, 300 mg groups, and in the placebo group), and invasive ductal breast carcinoma (0%, 1.3%, 0%, 0.4%, respectively in each group). ***Treatment-related serious TEAE***s were reported in 5 patients: cerebrovascular accident in 1 patient and myopathy in 1 other patient in the S201086/GLPG1972 150 mg group, suicidal depression in 1 patient in the 300 mg group, acute myocardial infarction in 1 patient and drug-induced liver injury in 1 other patient in the placebo group.

One ***fatal TEAE*** due to COVID-19, not related to treatment, was reported in the S201086/GLPG1972 150 mg group. This COVID-19 leading to death started 2 months after the last study drug intake.

TEAEs leading to treatment withdrawal were reported in 2 or less patients in all treatment groups, except arthralgia (3 patients in the S201086/GLPG1972 75 mg group), ALT increased and AST increased (3 patients in the S201086/GLPG1972 300 mg group for each event). ***Treatment-related TEAEs leading to treatment withdrawal*** were reported in not more than one patient, except the following reported in 2 patients: headache in the S201086/GLPG1972 75 mg group, arthralgia in the 75 mg and 300 mg groups, ALT increased in the 300 mg group, AST increased in the 300 mg group, nausea in the 300 mg group, and diarrhoea in the placebo group. ***Treatment-related serious TEAEs leading to treatment withdrawal*** were reported in 3 patients: cerebrovascular accident in 1 patient in the S201086/GLPG1972 150 mg group, suicidal depression in 1 patient in the 300 mg group, drug-induced liver injury in 1 patient in the placebo group.

- **Laboratory tests**

The most frequent treatment-emergent potentially clinically significant abnormalities (PCSA) **biochemical values** were detected for high GGT. Post-baseline high GGT values (> 3xULN) were observed across treatment groups with numerically higher incidences in the GLPG1972 300 mg (7.5%) and GLPG1972 75 mg (7.7%) group than in the placebo group (3.5%), but lower than in GLPG1972 150 mg group (0.9%). More than half of these subjects (29 out of 45) had GGT values above the ULN at baseline. Post-baseline high ALT values (> 3xULN) were observed in five subjects in the 300 mg GLPG1972 group (2.2%), in one subject in the 75 mg GLPG1972 group (0.4%) and in none of the subjects in the placebo group and 150 mg GLPG1972 group. Analyses of the mean over time for ALT showed a small transient increase at Week 8 in the 300 mg GLPG1972 group. The clinical relevance of this finding is yet to be determined.

Treatment-emergent PCSA **haematological values** were sparse in all treatment groups and for each parameter.

- **Other safety evaluation**

There was no relevant difference between the treatment groups in mean changes for body weight, blood pressure and heart rate during the study.

Clinically significant ECG abnormalities were reported with a similar frequency in the treatment groups.

There was no treatment-emergent QTcF value > 480 ms, except one value within]480 ; 500] ms in 1 patient in the S201086/GLPG1972 300 mg group at visit W028, and no significant change from baseline > 60 ms in any treatment group.

CONCLUSION

This study was a phase 2, international, multi-regional, multicentre, randomised, double-blind, parallel-group, placebo-controlled, dose-ranging study aimed to demonstrate the efficacy of at least one of the three doses of S201086/GLPG1972 compared to placebo after 52 weeks of treatment in reducing cartilage loss measured by cartilage thickness of the cMTFC of the target knee in patients diagnosed with knee OA.

The primary analysis showed that there was no statistically significant difference between any of the S201086/GLPG1972 groups *i.e.* 75 mg, 150 mg and 300 mg and the placebo group in the change from baseline to W052 in cartilage thickness of the cMTFC. Results are consistent through all the sensitivity analyses for handling of missing data and for delayed W052 qMRI assessment due to the COVID-19 pandemic. No statistically significant difference between any of the S201086/GLPG1972 groups and the placebo group was observed for any of the structural and clinical secondary endpoints considered. Overall, there was no relevant difference observed between any of the treatment groups and the placebo group, nor was there a dose trend.

S201086/GLPG1972 was generally safe and well tolerated. Overall, no clinically relevant differences were found between treatment groups in incidence of AEs, laboratory parameters, vital signs and ECG.

Date of the report: 05 March 2021

Version of the report: Final version