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Evaluation of S201086/GLPG1972, an ADAMTS-5 inhibitor, for the treatment of knee osteoarthritis in ROCCELLA: a phase 2 randomized clinical trial

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SUMMARY

Objective: To evaluate the efficacy and safety of the anti-catabolic ADAMTS-5 inhibitor S201086/GLPG1972 for the treatment of symptomatic knee osteoarthritis.
Design: ROCCELLA (NCT03595618) was a randomized, double-blind, placebo-controlled, dose-ranging, phase 2 trial in adults (aged 40–75 years) with knee osteoarthritis. Participants had moderate-to-severe pain in the target knee, Kellgren–Lawrence grade 2 or 3 and Osteoarthritis Research Society International joint space narrowing (grade 1 or 2). Participants were randomized 1:1:1:1 to once-daily oral S201086/GLPG1972 75, 150 or 300 mg, or placebo for 52 weeks. The primary endpoint was change from baseline to week 52 in central medial femorotibial compartment (cMFTC) cartilage thickness assessed quantitatively by magnetic resonance imaging. Secondary endpoints included change from baseline to week 52 in radiographic joint space width, Western Ontario and McMaster Universities Osteoarthritis Index total and subscores, and pain (visual analogue scale). Treatment-emergent adverse events (TEAEs) were also recorded.
Results: Overall, 932 participants were enrolled. No significant differences in cMFTC cartilage loss were observed between placebo and S201086/GLPG1972 therapeutic groups: placebo vs 75 mg, $P = 0.165$; vs 150 mg, $P = 0.939$; vs 300 mg, $P = 0.682$. No significant differences in any of the secondary endpoints were observed between placebo and treatment groups. Similar proportions of participants across treatment groups experienced TEAEs.
Conclusions: Despite enrolment of participants who experienced substantial cartilage loss over 52 weeks, during the same time period, S201086/GLPG1972 did not significantly reduce rates of cartilage loss or modify symptoms in adults with symptomatic knee osteoarthritis.

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Introduction

Osteoarthritis (OA) is the most common form of arthritis and is characterized by joint pain, activity limitation, reduced health-related quality of life and excess mortality[1,2]. However, despite its prevalence, no disease-modifying OA drugs (DMOADs) have been approved by either the US Food and Drug Administration or the European Medicines Agency[3–8].

OA is characterized by changes in the subchondral bone[9,10] and progressive degradation of articular cartilage[11,12]. Aggrecan is a major structural component of the articular cartilage extracellular matrix[11–15]. The aggrecanase, 'a disintegrin and metalloproteinase with thrombospondin motif-5' (ADAMTS-5), is responsible for aggrecan cleavage[16], and is upregulated in OA[11,15,17]. Inhibition of the aggrecanase activity of ADAMTS-5 is considered a potential therapeutic target for the treatment of OA[14,17,18].

S201086/GLPG1972 is a potent and highly selective inhibitor of ADAMTS-5 in development for the treatment of OA. S201086/GLPG1972 successfully inhibited ADAMTS-5-driven aggrecan degradation in mouse and human cartilage explants and significantly decreased cartilage degradation when administered orally to rodents with surgery-induced OA (by meniscal transection in rats and destabilization of medial meniscus in mice)[19]. Furthermore, the safety, pharmacokinetics and pharmacodynamics of S201086/GLPG1972 were investigated in a first-in-human randomized, placebo-controlled study in healthy men (ClinicalTrials.gov: NCT02612246), as well as in men and women with knee or hip OA (ClinicalTrials.gov: NCT03311009) in whom S201086/GLPG1972 was found to be generally well tolerated and to significantly reduce the aggrecanase activity of ADAMTS-5 vs placebo[20].

The aim of the present phase 2 trial was to evaluate the efficacy, in terms of slowing cartilage loss and improving symptoms, and safety of three doses of S201086/GLPG1972 vs placebo in participants with knee OA.

Methods

Study design

ROCCELLA was a randomized, double-blind, placebo-controlled, dose-ranging phase 2 trial carried out in 12 countries between 14 August 2018 and 14 July 2020 (ClinicalTrials.gov: NCT03595618). The full methodology of the trial has been described previously[21]. Briefly, the trial comprised a 5-week screening period and a 52-week double-blind treatment period followed by a 2-week safety follow-up period. Baseline was defined as the last assessment before the first treatment. Clinic visits were every 4–12 weeks. Treatment was discontinued at week 52 and participants attended an end-of-study visit 2 weeks after their last dose. In cases of early discontinuation, participants underwent an early withdrawal visit followed by an end-of-study visit 2 weeks later, unless they withdrew consent. The schedule of study procedures is given in Table S1.

Participants were randomly assigned 1:1:1:1 to S201086/GLPG1972 75, 150 or 300 mg, or placebo orally once daily[21]. Randomization was stratified by geographical zone (Japan, South Korea/Taiwan and rest of the world). All participants provided written informed consent, and the final protocol and two protocol amendments (three amendments in the USA and Brazil) were reviewed and approved by the institutional review board or independent ethics committee at each participating centre. The trial was performed in accordance with the ethical principles of the Declaration of Helsinki.

Participants

Participants between 40 and 75 years of age, with body weight >40 kg and body mass index <40 kg/m^2, who met eligibility criteria were included. Participants had to have a clinical diagnosis of knee OA and fulfil clinical and radiological American College of Rheumatology classification criteria for knee OA[22], and have knee pain for ≥6 months and on most days in the month before screening. Participants were included if they had pain between 40 and 90 mm on a 100 mm visual analogue scale (VAS) in the same knee at both screening and baseline. Additionally, participants' target knees had to show, based on the central reading of a knee X-ray taken at screening, predominantly medial compartment radiographic disease (medial femorotibial joint space narrowing [JSN] > lateral JSN), and meet the following radiographic severity criteria: Kellgren–Lawrence (KL) grade 2 or 3 and Osteoarthritis Research Society International (OARSI) medial JSN grade 1 or 2. JSN was graded for degree of change from 0 to 3 (0 = normal, 1 = mild change, 2 = moderate change, 3 = severe change), as per OARSI atlas criteria[23]. All radiographic knee assessments were based on posteroanterior fixed flexion weight-bearing X-rays (Synaflexer positioning frame)[21,24]. Radiograph readings were conducted by experienced musculoskeletal radiologists. Complete inclusion and exclusion criteria have been published elsewhere[21].

Patient and public involvement

The study participants and the public were not involved in the design or conduct of ROCCELLA or in the reporting or dissemination of the study data.

Objectives and endpoints

The primary objective was to demonstrate the efficacy of at least one dose of S201086/GLPG1972 in reducing cartilage loss in the target knee vs placebo after 52 weeks of treatment. Primary and secondary efficacy endpoints were recorded in the target knee. The primary efficacy endpoint was change from baseline to week 52 in central medial femorotibial compartment (cMFTC)[25] cartilage thickness, measured quantitatively through a blinded, quality-controlled, central readout of standardized, quality-controlled magnetic resonance imaging (MRI) data[21,26]. Cartilage segmentation was performed manually by seven experienced readers (with ≥11 years of experience with manual cartilage analysis at the start of the study). All segmentations were quality-controlled by one of two experienced experts, and the cartilage segmentation was corrected by the readers after quality checks, when appropriate. Further details of MRI acquisition and assessment are provided elsewhere[21] and in Supplementary Material 1. The root-mean square standard deviation (SD) and coefficient of variation were determined to assess the intra-reader test–retest reliability[27].

Secondary structural endpoints included change from baseline to week 52 in radiographic medial joint space width (JSW) by fixed location assessment (at $x = 0.25$), and the proportion of participants who had prespecified cartilage loss in the cMFTC of ≥8% at week 52 (herein called "structural progressors") as assessed by MRI. Additional secondary structural endpoints (each assessed by MRI) included change from baseline to week 52 in cartilage thickness of the total femorotibial compartment (tFTC) and change from baseline to weeks 28 and 52 in subchondral bone area of the medial femoral condyle surface.

Clinical secondary endpoints were change from baseline to week 52 in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score and subscale scores of function, pain and stiffness; change from baseline to week 52 in pain using a 100 mm VAS; change from baseline to week 52 in patient global assessment (PGA) of disease activity using a 100 mm VAS; the proportion of participants who achieved an Outcome Measures in Rheumatology (OMERACT)-OARSI response at week 52[28]; and participants' use of analgesics for treatment of knee pain at each

study visit. Change from baseline to week 52 in bone shape as measured by MRI was assessed as an exploratory endpoint.

Safety endpoints included the occurrence of treatment-emergent adverse events (TEAEs) and serious TEAEs. Additionally, changes over time in vital signs, laboratory values, physical examinations, body weight and electrocardiogram (ECG) parameters were recorded.

Statistical analyses

In total, 852 participants (213 per treatment group) were expected to provide a minimal power of 70% to conclude that at least one dose of S201086/GLPG1972 was superior to placebo, with a difference of 0.0825 mm (SD, 0.30 mm) in the primary endpoint at a two-sided significance level of 5%, using analysis of covariance (ANCOVA) adjusted for multiple testing by a Dunnett procedure. A treatment effect of 0.0825 mm corresponds to 75% of the expected cartilage loss in the placebo group (0.11 mm over 1 year)[6,21].

The modified randomized set consisted of all included participants to whom a therapeutic unit was randomly assigned using an interactive web response system; this set was used for all efficacy analyses. Participants were analysed according to the randomized treatment. The safety set included all participants who took at least one dose of S201086/GLPG1972 or placebo; the safety set was used for all safety analyses according to the treatment received by participants at inclusion.

The primary endpoint, change from baseline to week 52 in cMFTC cartilage thickness, was evaluated using a restricted maximum likelihood-based, mixed-effects model for repeated measures using all longitudinal observations at each postbaseline visit, preceded by a multiple imputation step for participants without a postbaseline measurement. Sensitivity analyses for the management of missing data and for delayed week 52 MRI data owing to the COVID-19 pandemic were performed to evaluate the robustness of the results of the primary analysis. To account for the multiplicity of comparisons associated with multiple doses, a Dunnett procedure was used for primary and secondary endpoints. There was no multiplicity adjustment for analyses of multiple secondary endpoints.

Change from baseline to week 52 in cartilage thickness of the tFTC, change from baseline to week 52 in subchondral bone area of the medial femoral condyle surface of the target knee, WOMAC scores, VAS pain and PGA disease activity were evaluated using the same method as the primary endpoint. Differences between treatment groups in the proportion of structural progressors at week 52 and the proportion of participants who achieved an OMERACT-OARSI response were analysed using a logistic model, preceded by a multiple imputation step for missing data. Comparisons between treatment groups for changes in subchondral bone area of the medial femoral condyle of the target knee from baseline to week 28 and in JSW from baseline were assessed using an ANCOVA model. Safety data were analysed for all participants in the safety set and were reported using descriptive statistics. Statistical analyses were carried out using SAS software version 9.4.

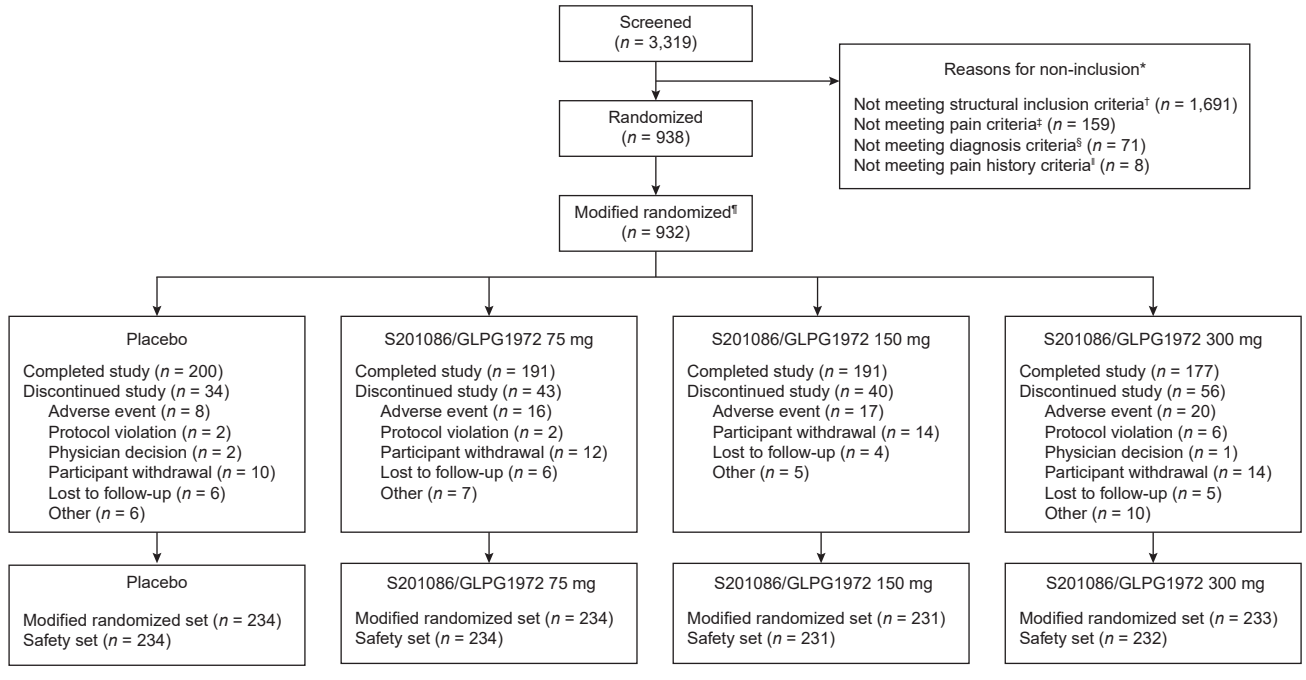

Fig. 1

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Participant disposition. One serious, fatal TEAE due to COVID-19 was reported in the S201086/GLPG1972 150 mg group; COVID-19 started 2 months after the last treatment intake. *Participants could have not been included in the trial for more than one reason. †Based on a fixed flexion weight-bearing X-ray of the target knee and a central readout of: predominant medial compartment radiographic disease; KL grade 2 or 3; and OARSI grade 1 or 2 medial tibiofemoral joint space narrowing. ‡≥40 mm and ≤90 mm on a 100 mm VAS. §Based on the clinical and radiological criteria of the ACR. ‖Knee pain for ≥6 months and on most days during the preceding month. ¶A total of six participants were randomized to treatment but did not receive the study drug and were not included in the modified randomized set. ACR: American College of Rheumatology; KL: Kellgren–Lawrence; OARSI: Osteoarthritis Research Society International; VAS: visual analogue scale.

Results

Baseline demographics and characteristics

Overall, 3,319 participants from 12 countries underwent screening and 932 were randomized (placebo, $n = 234$; 75 mg, $n = 234$; 150 mg, $n = 231$; 300 mg, $n = 233$; Fig. 1). The numbers of participants randomized by country are given in Table S2. Baseline demographics and characteristics were similar across treatment groups (Table I). The mean (SD) age of participants was 62.9 (7.3) years and most (69.3%) were women. In total, 88.8% of target knees were KL grade 3, and 67.3% had medial OARSI JSN grade 2. The overall mean (SD) time since diagnosis was 7.2 (6.9) years. In total, 173 participants discontinued the study (placebo, $n = 34/234$ [14.5%]; 75 mg, $n = 43/234$ [18.4%]; 150 mg, $n = 40/231$ [17.3%]; 300 mg, $n = 56/233$ [24.0%]; Fig. 1).

Cartilage loss in the cMFTC

In all treatment groups, target knees demonstrated substantial cartilage loss from baseline to week 52. The mean (95% confidence interval [CI]) change in cMFTC cartilage thickness was greatest in the placebo group (−0.12 [−0.16 to −0.07] mm), followed by the S201086/GLPG1972 150 mg (−0.10 [−0.14 to −0.06] mm), 300 mg (−0.09 [−0.12 to −0.05] mm) and 75 mg (−0.07 [−0.10 to −0.04] mm) groups. No statistically significant differences in cMFTC cartilage thickness loss were observed between the placebo and S201086/GLPG1972 treatment groups (placebo vs 75 mg, treatment effect estimate [E] = 0.045 [95% CI −0.003 to 0.093], $P = 0.165$; vs 150 mg, $E = 0.012$ [95% CI −0.039 to 0.063], $P = 0.939$; vs 300 mg, $E = 0.023$ [95% CI −0.026 to 0.073], $P = 0.682$; Table II). These results were confirmed by sensitivity analyses for delayed MRI at week 52 owing to the COVID-19 pandemic (Fig. S1), and for the management of missing data. *Post hoc* analyses of OMERACT-OARSI responders vs non-responders did not reveal any significant differences in baseline characteristics between the two groups (data not shown). The study-specific test–retest precision has also been reported previously[27].

Structural secondary endpoints

In all groups, mean radiographic JSW decreased between baseline and week 52 (Table II), with no significant differences in change in JSW observed between the placebo group and any of the S201086/GLPG1972 treatment groups. The proportions of structural progressors at week 52 were similar between groups (placebo, 20.3%; 75 mg, 13.6%; 150 mg, 21.5%; 300 mg, 16.6%), and were not significantly different when comparing S201086/GLPG1972 treatment groups with placebo (Table II). Change from baseline in cartilage thickness of the tFTC and change from baseline in the bone area of the medial femoral condyle surface were not significantly different between S201086/GLPG1972 and placebo groups (Table S3).

Demographic/characteristic	Placebo ($n = 234$)	S201086/GLPG1972 75 mg ($n = 234$)	S201086/GLPG1972 150 mg ($n = 231$)	S201086/GLPG1972 300 mg ($n = 233$)
Age, mean (SD), years	63.3 (7.1)	62.9 (7.5)	63.2 (7.2)	62.1 (7.4)
Age, *n* (%), years				
≥40–54	28 (12.0)	31 (13.2)	29 (12.6)	33 (14.2)
≥55–64	95 (40.6)	94 (40.2)	96 (41.6)	97 (41.6)
≥65	111 (47.4)	109 (46.6)	106 (45.9)	103 (44.2)
Women, *n* (%)	163 (69.7)	164 (70.1)	165 (71.4)	154 (66.1)
Race, *n* (%)				
White	171 (73.1)	167 (71.4)	177 (76.6)	168 (72.1)
Asian	32 (13.7)	31 (13.2)	28 (12.1)	30 (12.9)
Black or African American	25 (10.7)	27 (11.5)	19 (8.2)	25 (10.7)
Multiple	6 (2.6)	8 (3.4)	6 (2.6)	8 (3.4)
American Indian, native Alaskan or native Hawaiian or other Pacific Islander	0	1 (0.4)	1 (0.4)	2 (0.9)
Time since first diagnosis, mean (SD), years	7.3 (6.7)	6.9 (6.4)	7.6 (7.4)	7.1 (7.2)
KL grade, *n* (%)				
2	29 (12.4)	15 (6.4)	30 (13.0)	29 (12.4)
3	205 (87.6)	219 (93.6)	200 (86.6)	204 (87.6)
4	0	0	1 (0.4)	0
Medial compartment OARSI JSN grade, *n* (%)				
0	0	1 (0.4)	1 (0.4)	0
1	70 (29.9)	74 (31.6)	73 (31.6)	84 (36.1)
2	164 (70.1)	159 (67.9)	156 (67.5)	148 (63.5)
3	0	0	1 (0.4)	1 (0.4)
Cartilage thickness in cMFTC, mean (SD), mm	3.19 (0.82)	3.25 (0.76)	3.23 (0.76)	3.33 (0.80)
Joint space width, mean (SD), mm	2.48 (0.86)	2.50 (0.78)	2.50 (0.78)	2.58 (0.84)
WOMAC total score, mean (SD)	48.3 (14.5)	48.0 (15.2)	48.7 (15.0)	47.0 (15.2)
Pain (VAS), mean (SD)	63.5 (11.0)	63.3 (11.4)	63.8 (11.5)	63.3 (12.1)
PGA (VAS), mean (SD)	50.4 (19.2)	47.1 (18.3)	47.9 (19.0)	49.4 (17.5)

cMFTC: central medial femorotibial compartment; JSN: joint space narrowing; KL: Kellgren–Lawrence; OARSI: Osteoarthritis Research Society International; PGA: patient global assessment; SD: standard deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table I

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Baseline demographics and characteristics

Endpoints	Placebo ($n = 234$)	S201086/GLPG1972 75 mg ($n = 234$)	S201086/GLPG1972 150 mg ($n = 231$)	S201086/GLPG1972 300 mg ($n = 233$)
Primary endpoint				
Cartilage thickness in cMFTC, mm				
Change from baseline at week 52				
Number of participants	172	162	158	151
Mean (SD)	−0.116 (0.273)	−0.068 (0.202)	−0.097 (0.268)	−0.085 (0.217)
Treatment effect at week 52				
E (SE)	–	0.045 (0.025)	0.012 (0.026)	0.023 (0.025)
95% CI	–	−0.003 to 0.093	−0.039 to 0.063	−0.026 to 0.073
P value	–	0.165	0.939	0.682
Structural secondary endpoints				
Joint space width, mm				
Change from baseline at week 52				
Number of participants	179	169	163	155
Mean (SD)	−0.174 (0.470)	−0.087 (0.397)	−0.167 (0.506)	−0.113 (0.464)
Treatment effect at week 52				
E	–	0.095	0.016	0.075
95% CI	–	−0.003 to 0.193	−0.086 to 0.118	−0.029 to 0.179
P value	–	0.141	0.981	0.349
Proportion of structural progressors*				
Number of participants	172	162	158	151
Progressor at week 52, *n* (%)	35 (20.3)	22 (13.6)	34 (21.5)	25 (16.6)
Treatment effect at week 52				
E	–	1.47	0.89	1.08
95% CI	–	0.8 to 2.6	0.5 to 1.5	0.6 to 1.8
P value	–	0.396	0.951	0.985

CI: confidence interval; cMFTC: central medial femorotibial compartment; E: treatment effect estimate; OA: osteoarthritis; SD: standard deviation; SE: standard error.
* Defined as a patient who had ≥8% cartilage loss in the cMFTC between baseline and week 52.

Table II

Summary of primary and key secondary structural endpoints in participants with knee OA

Osteoarthritis and Cartilage

Clinical secondary endpoints

There were no significant differences between any of the S201086/GLPG1972 groups and the placebo group for each of the clinical secondary endpoints (Table III, Fig. 2, Tables S4 and S5). These results were confirmed by sensitivity analyses assessing treatment effect at week 40 (with <1% of visits impacted by the COVID-19 pandemic). In addition, completer analyses revealed no differences between treatment groups in the primary or secondary endpoints (data not shown).

Exploratory endpoint

No differences in change from baseline to week 52 in bone shape were detected between treatment groups (data not shown).

Safety

Mean (SD) treatment duration was 46.7 (13.8) weeks and mean (SD) compliance with study treatment was 89.1% (14.5%), with similar results observed across all groups. Serious TEAEs occurred in similar proportions of participants across treatment groups (Table IV). One serious, fatal TEAE due to COVID-19 was reported in the S201086/GLPG1972 150 mg group; COVID-19 started 2 months after the last treatment intake.

TEAEs were experienced by similar proportions of participants across treatment groups (Table IV). The most common TEAEs in the placebo and S201086/GLPG1972 75, 150 and 300 mg groups were arthralgia (8.1%, 11.5%, 15.2% and 11.2%, respectively), nasopharyngitis (8.5%, 9.0%, 6.9% and 9.5%, respectively) and fall (5.6%, 6.4%, 8.7% and 6.9%, respectively; Table IV). The proportion of participants experiencing back pain was lower in those receiving S201086/GLPG1972 (75 mg, 4.7%; 150 mg, 4.3%; 300 mg, 3.0%) than in those receiving placebo (8.1%). A numerically greater proportion of participants receiving S201086/GLPG1972 300 mg had AE reports of increased gamma-glutamyl transferase compared with those receiving placebo and S201086/GLPG1972 75 and 150 mg (6.9% vs 1.7%, 1.3% and 0.9%, respectively). No structural joint-specific AEs were observed in the study.

Slightly higher proportions of patients in the three S201086/GLPG1972 dose groups withdrew from treatment owing to TEAEs (75 mg, 6.8%; 150 mg, 7.4%; 300 mg, 8.6%) than in the placebo group (3.8%) (Table IV). Individual TEAEs leading to treatment withdrawal were reported in two or fewer participants in all treatment groups, except arthralgia (three participants in the S201086/GLPG1972 75 mg group) and increased alanine aminotransferase and increased aspartate aminotransferase (three participants in the S201086/GLPG1972 300 mg group for each event). Participants in the S201086/GLPG1972 300 mg group experienced a small transient increase in mean alanine aminotransferase at week 8. One participant in Brazil who received placebo met Hy's law.

No clinically relevant differences were observed between groups in mean changes for body weight, heart rate, blood pressure and ECG parameters during the trial (Table S6).

Discussion

The international, randomized, double-blind, placebo-controlled, dose-ranging phase 2 ROCCELLA trial used state-of-the-art methodology to determine whether at least one dose of the

Endpoints	Placebo ($n = 234$)	S201086/GLPG1972 75 mg ($n = 234$)	S201086/GLPG1972 150 mg ($n = 231$)	S201086/GLPG1972 300 mg ($n = 233$)
Clinical secondary endpoints				
WOMAC total score				
Change from baseline at week 52				
Number of participants	200	189	187	176
Mean (SD)	−18.4 (18.9)	−16.3 (17.7)	−16.9 (17.7)	−16.1 (19.8)
Treatment effect at week 52				
E (SE)	–	−2.1 (1.7)	−1.9 (1.8)	−1.9 (1.8)
95% CI	–	−5.6 to 1.3	−5.4 to 1.5	−5.3 to 1.6
P value	–	0.467	0.557	0.593
Pain (VAS)				
Change from baseline at week 52				
Number of participants	199	191	185	178
Mean (SD)	−28.9 (25.0)	−27.2 (24.3)	−25.6 (26.9)	−28.2 (27.1)
Treatment effect at week 52				
E (SE)	–	−2.2 (2.5)	−4.1 (2.5)	−1.1 (2.5)
95% CI	–	−7.1 to 2.7	−9.0 to 0.8	−6.1 to 3.9
P value	–	0.705	0.243	0.949
PGA (VAS)				
Change from baseline at week 52				
Number of participants	200	191	187	178
Mean (SD)	14.0 (31.3)	19.4 (30.0)	14.3 (30.7)	14.1 (28.4)
Treatment effect at week 52				
E (SE)	–	1.4 (2.5)	−2.3 (2.5)	0.1 (2.5)
95% CI	–	−3.4 to 6.3	−7.1 to 2.6	−4.8 to 5.0
P value	–	0.890	0.682	1.000
Proportion of OMERACT-OARSI responders				
Number of participants	200	189	187	176
Responder at week 52, n (%)	127 (63.5)	125 (66.1)	119 (63.6)	103 (58.5)
Treatment effect at week 52				
E	–	1.05	0.95	0.82
95% CI	–	0.7 to 1.6	0.6 to 1.4	0.6 to 1.2
P value	–	0.991	0.992	0.653

CI: confidence interval; E: treatment effect estimate; OA: osteoarthritis; OMERACT-OARSI: Outcome Measures in Rheumatology–Osteoarthritis Research Society International; PGA: patient global assessment; SD: standard deviation; SE: standard error; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table III

Osteoarthritis and Cartilage

Summary of key secondary clinical endpoints in participants with knee OA

ADAMTS-5 inhibitor S201086/GLPG1972 slows cartilage loss in participants with knee OA at high risk of cartilage loss. After 52 weeks, no significant differences in cMFTC cartilage thickness in the target knee were detected between any of the S201086/GLPG1972 groups and the placebo group. In addition, no differences between treatment groups in any of the secondary structural or clinical endpoints were observed.

One of the key challenges for DMOAD trials has been the selection of appropriate patient populations for detection of a treatment effect[29,30]. Recently, there has been a shift toward identifying study participants with advanced radiographic OA and elevated pain. In a *post hoc* analysis of the sprifermin phase 2 trial, for example, a subgroup of participants at high risk of disease progression had a structural response to treatment, which translated into symptomatic clinical benefit[31]. In ROCCELLA, selection criteria were based on previous studies of cartilage loss over time[25,32–34], and meant that more participants with KL grade 3 than grade 2 knees were included. Participants did, however, have cartilage present, as shown by the mean baseline cartilage thickness values (placebo, 3.19 mm; 75 mg, 3.25 mm; 150 mg, 3.23 mm; 300 mg, 3.33 mm). Cartilage loss in the placebo group was in line with that expected for knees of that radiographic severity, and was notably greater than that observed in the placebo group of the sprifermin FORWARD study[5]. Cartilage thickness was measured in the medial compartment of the knee, since this carries the highest weight-bearing burden and is the compartment where cartilage loss is most likely to occur[35]. ROCCELLA was powered to detect a moderate to large effect size to increase the likelihood that any treatment effect on cartilage loss detected would be associated with a clinically meaningful improvement in symptoms.

The availability of reliable imaging technologies is a requirement for the accurate assessment of structural outcomes in DMOAD trials. It is also important to consider the method of measurement (e.g., quantitative vs semi-quantitative), as well as different definitions of full-thickness cartilage loss, when interpreting changes to cartilage thickness in different patient cohorts. For example, the MOST study included whole-organ MRI score (WORMS) grade 5 (multiple areas of full-thickness loss or grade 2.5 lesions wider than 1 cm but <75% of the region) in their definition of widespread full-thickness cartilage damage[36]. In comparison, our study reported the number of participants who displayed full-thickness cartilage loss (presence of denuded areas of subchondral bone) throughout the entire central medial tibia and central region of the central medial femur subregions. These differences in definition of full-thickness cartilage loss very likely contribute to differences in the percentage of participants with full-thickness cartilage damage

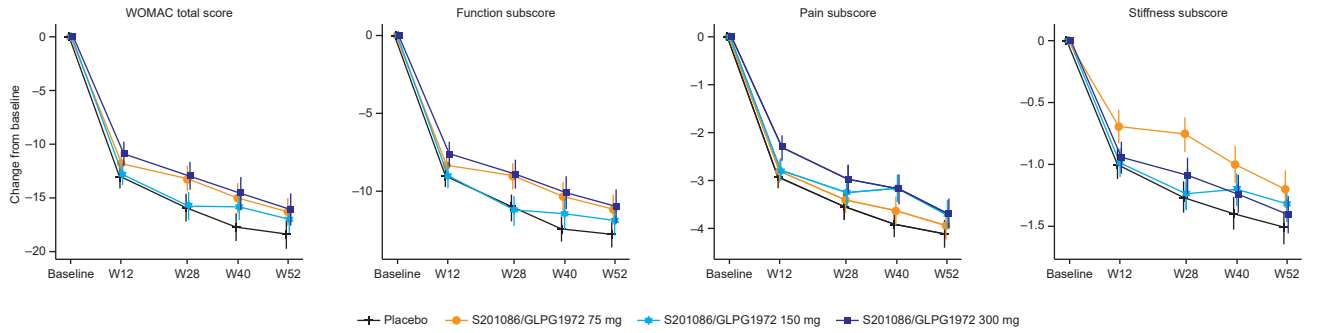

Fig. 2

Osteoarthritis and Cartilage

Mean (standard error) change over time in WOMAC total score and subscale scores. *Numbers of participants in the placebo, S201086/GLPG1972 75, 150 and 300 mg groups, respectively, with data at baseline: 234, 233, 230 and 231. Numbers of participants in the placebo, S201086/GLPG1972 75, 150 and 300 mg groups, respectively, with data for change from baseline: 222, 221, 212 and 211 (week 12); 216, 206, 199 and 189 (week 28); 209, 198, 194 and 182 (week 40); 200, 189, 187 and 176 (week 52). *Negative changes represent improvements in function, pain and stiffness. The scores ranged from 0 to 96 for the total score, and 0 to 86, 0 to 20 and 0 to 8 for the function, pain and stiffness subscale scores, respectively. Full data are given in Table S4. W: week; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

between this and the MOST study[36]. Until recently, measurements of structural changes in patients with OA relied upon conventional radiography. Though radiography can be used to detect osseous changes, such as changes in osteophytes, JSN, sclerosis, cysts and bone attrition, these features are not normally considered treatment targets in clinical trials[37]. Furthermore, JSN is only a surrogate marker of cartilage loss[38,39]. In the present trial, we used state-of-the-art quantitative MRI assessment of cartilage loss, with rigorous quality controls on image acquisition and central reading, to enhance the reliability of our results[21].

Further considerations for DMOAD evaluation include the mechanism of drug action and the nature of the disease. OA is a heterogeneous disorder with multiple phenotypes that may result from distinct and complex molecular mechanisms[30,40]. Each of

Events, *n* (%)	Placebo (*n* = 234)	S201086/GLPG1972 75 mg (*n* = 234)	S201086/GLPG1972 150 mg (*n* = 231)	S201086/GLPG1972 300 mg (*n* = 232)
Deaths	0	0	1 (0.4)*	0
TEAEs	174 (74.4)	174 (74.4)	177 (76.6)	174 (75.0)
Severe TEAEs†	29 (12.4)	25 (10.7)	27 (11.7)	30 (12.9)
Treatment-related TEAEs	37 (15.8)	36 (15.4)	30 (13.0)	47 (20.3)
Serious TEAEs	18 (7.7)	17 (7.3)	17 (7.4)	18 (7.8)
Serious treatment-related TEAEs	2 (0.9)	0	2 (0.9)	1 (0.4)
TEAEs leading to drug withdrawal	9 (3.8)	16 (6.8)	17 (7.4)	20 (8.6)
TEAEs occurring in ≥5% of participants				
Arthralgia	19 (8.1)	27 (11.5)	35 (15.2)	26 (11.2)
Nasopharyngitis	20 (8.5)	21 (9.0)	16 (6.9)	22 (9.5)
Fall	13 (5.6)	15 (6.4)	20 (8.7)	16 (6.9)
Back pain	19 (8.1)	11 (4.7)	10 (4.3)	7 (3.0)
Headache	9 (3.8)	15 (6.4)	12 (5.2)	11 (4.7)
Hypertension	16 (6.8)	6 (2.6)	9 (3.9)	12 (5.2)
Osteoarthritis	10 (4.3)	8 (3.4)	12 (5.2)	11 (4.7)
Increased blood creatine phosphokinase	8 (3.4)	12 (5.1)	7 (3.0)	9 (3.9)
Upper respiratory tract infection	10 (4.3)	7 (3.0)	12 (5.2)	6 (2.6)
Increased gamma-glutamyl transferase	4 (1.7)	3 (1.3)	2 (0.9)	16 (6.9)

TEAE: treatment-emergent adverse event.
* Fatal event due to COVID-19, which started 2 months after the last study treatment intake.
† Common Terminology Criteria for Adverse Events grade 3.

Table IV

Osteoarthritis and Cartilage

Summary of safety outcomes

these mechanisms may require a different, targeted therapy. In pharmacological studies, S201086/GLPG1972 successfully inhibited ADAMTS-5-driven aggrecan degradation in mouse and human cartilage explants, and significantly reduced cartilage degradation in an animal model of OA[19]. However, animal models of OA do not necessarily accurately reflect human disease pathology[41]. S201086/GLPG1972 100, 200 and 300 mg also significantly decreased plasma concentrations of alanine-arginine-glycine-serine fragments vs placebo in participants with knee or hip OA in a phase 1 study, confirming target engagement of the drug[20]. That study, though, was not designed to assess the effect of S201086/GLPG1972 on joint cartilage. In the present trial, despite having successfully selected a large number of participants with a high likelihood of cartilage loss, the anti-catabolic effect of 12 months of treatment with S201086/GLPG1972 on cartilage loss was below what was expected. Failure of the study drug to reach the target tissue following oral administration, however, cannot be excluded. It remains unknown whether aggrecanase inhibition was strong enough with S201086/GLPG1972, and thus if this single target approach would be sufficient to prevent cartilage loss in humans, or whether a multifactorial strategy is required. There is also the possibility that the trial was too short to determine a treatment effect.

Despite the strengths of our study, there were some limitations. Detailed semi-quantitative assessment of structural joint pathology was not undertaken, as the current study relied on quantitative analysis of articular cartilage as a structural outcome. In ROCCELLA, no clinical benefit of S201086/GLPG1972 on pain was demonstrated. A complex issue for long-term DMOAD trials is the requirement (on ethical grounds) for use of concomitant analgesics. Although analgesics were used by similar proportions of patients across treatment groups during our study, the confounding effect of their use may have diminished any differences in clinical outcomes that otherwise may have been observed. Only participants with a consistent pain signal at screening and baseline were enrolled in the study, with the aim of reducing floor and ceiling effects. Nevertheless, not all possible preventive measures were taken to increase sensitivity to changes in pain, for example, washout of analgesic medications was not required before assessment of clinical endpoints. Furthermore, it may be difficult to demonstrate that slowing of structural progression and reduction of pain occur at the same time[40,42]. Indeed, while sprifermin and the cathepsin K inhibitor MIV-711 have been shown to reduce cartilage loss, these drugs had no significant effect on pain in their respective trials[5,8].

A promising approach for future DMOAD trials may be using OA biomarkers to identify subgroups of patients who are likely to respond to a particular treatment[18,42,43]. Several structural phenotypes have been proposed, with MRI-based screening or simplified eligibility assessments potentially able to help streamline identification of patients with these phenotypes. Nevertheless, these phenotypes are rarely mutually exclusive and likely overlap[44]. Thus, progress is still to be made in delineating OA endotypes and/or phenotypes, and in understanding how these may affect responses to treatments and prevention strategies[45].

ROCCELLA was a large, international, placebo-controlled, dose-ranging trial that assessed the safety and efficacy of the novel ADAMTS-5 inhibitor, S201086/GLPG1972, in the treatment of knee OA. The trial successfully enrolled a large population with knee OA that experienced detectable cartilage loss over time. Despite this, S201086/GLPG1972 was not efficacious in reducing cMFTC cartilage loss or in improving function or pain in the target knee. S201086/GLPG1972 was generally well tolerated, and no safety signals were identified. Lessons from this and other DMOAD trials could be applied to future trials of anti-catabolic agents in OA. Nevertheless, considerations for alternative trial designs may be warranted for the development of successful knee OA treatments[46].

Contributions

TS contributed to data acquisition and interpretation. MP and HD contributed to the conception and design of the study, and analysis and interpretation of the data. EvdA contributed to study design and data interpretation. KB contributed to the conception and design of the study, and analysis and interpretation of the data. SH contributed to study design and data acquisition and interpretation. MvdS and SG contributed to the conception and design of the study, and analysis and interpretation of the data. DP contributed to analysis and interpretation of the data. OI contributed to the conception and design of the study, and analysis and interpretation of the data. DC, KM, MCH, HB and WW contributed to the analysis and interpretation of the data. FE and PGC contributed to the conception and design of the study, and analysis and interpretation of the data.

All authors* contributed to manuscript development and approved the final draft for submission.

*FE was unable to approve the final draft of this manuscript, but contributed substantially to the development of the manuscript and the ROCCELLA study, and fulfilled the majority of the authorship criteria described by the International Committee of Medical Journal Editors.

Declaration of competing interest

TS has received consultancy fees from AstraZeneca, Collegium, Galapagos NV, GSK, Lilly, Pfizer and Vertex, and is an employee of Northwestern University Feinberg School of Medicine, which has also received fees from Galapagos NV. MP, KB, SG, OI and DC are employees of Institut de Recherches Internationales Servier (IRIS). EvdA, MvdS, DP and KM are employees and shareholders of Galapagos NV. HD and SH were employees and shareholders of Galapagos NV at the time of the study. MCH has received consultancy fees from Acadia Pharmaceuticals, Bioclinica, BriOri Biotech, Eli Lilly, Flexion Therapeutics Inc., GSK, Novartis Pharma AG, Pfizer Inc and Theralogix LLC, and was a member of the ROCCELLA Data and Safety Monitoring Board. HB has received research grants from Galapagos NV. The Parker Institute, Bispebjerg, and Frederiksberg Hospital are supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). WW is a part-time employee and shareholder of Chondrometrics, and has received personal fees from Galapagos NV. FE has received grants from Galapagos NV and personal fees from AbbVie, Galapagos NV, HealthLink, ICM, IRIS, Kolon TissueGene, Merck KGaA, Novartis, Roche and Samumed. PGC has received consultancy fees from AbbVie, BMS, EMD Serono, Flexion Therapeutics, Galapagos, GSK, Gilead, Novartis, Pfizer, Regeneron, Stryker and UCB; and speakers fees from AbbVie, Galapagos and Pfizer.

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Data sharing statement

Anonymized individual patient data will not be shared. Aggregate data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data and its intended use.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2023.04.001.

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