1. TITLE PAGE

An Exploratory, Double-Blind, Randomized, Placebo and Active-Controlled Study to Assess the Safety and Efficacy of RGH-478 for the Treatment of Moderate to Severe Pain in Osteoarthritis of the Knee

Study design: Phase II exploratory, randomized, double-blind, placebo and active control, 3-arm, multicenter study in patients with moderate to severe pain from knee OA

Sponsor:
Gedeon Richter Plc.
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Study code: [redacted]
Phase of development: Phase II.

Study period:
Study start: 16 SEP 2011 **Study end: 08 AUG 2012**

Study supervisor:
[redacted]

Clinical report compiled by:
[redacted]

Date of the report: 27 FEB 2021
(Final clinical report)

The study was performed according to the principles of ICH-GCP.

2. SYNOPSIS

Study title:	An Exploratory, Double-Blind, Randomized, Placebo and Active-Controlled Study to Assess the Safety and Efficacy of RGH-478 for the Treatment of Moderate to Severe Pain in Osteoarthritis of the Knee
Phase of development:	Phase 2
Study centers:	The study protocol envisaged 25 sites in Hungary. Of the planned 25 sites eventually 17 sites were opened in Hungary.
Study objective:	The primary objective was to evaluate the efficacy of RGH-478 compared with placebo in patients with osteoarthritis (OA). The secondary objectives of this study were to assess the safety and tolerability of RGH-478 in patients with OA.
Study design:	This was an exploratory, randomized, double-blind, placebo and active control, 3-arm, multicenter Phase II study in patients with moderate to severe pain from knee OA.
Duration of the study:	The study consisted of a Screening Period, a Treatment Period, and a Follow-up Period. The Screening Period comprised of a Washout Period followed by a Run-In Period. After completion of the washout, patients entered a Run-In Period lasted 2 to 5 days prior to the baseline visit (V2). After successful completion of the Screening Period, patients were randomized at the baseline visit (V2) to one of the 3 study treatment arms and entered a 4-week Treatment Period. Patients attended the study clinic for a total of 6 scheduled visits, including the screening visit and a follow up post-study visit (PSV). Patients were enrolled in the study and randomized to study treatments at V2 that should have taken place a minimum of 4 days after the initial screening visit (V1). During the treatment period, V3 and V4 took place 7 (or ± 1) days and 14 (or ± 1) days after V2, respectively; V5 took place 28 (or -2) days after V2, at the end of the treatment period. The PSV took place 7 to 10 days after completion of study treatment.
Sample size:	A total of 248 patients (of whom 4 patients did not receive IMP) were randomized in a 2:2:1 allocation ratio to RGH-478, Placebo, or Celecoxib (98 patients were receiving RGH-478, 98 patients were receiving placebo, and 52 patients were receiving Celecoxib).

Investigational product, dose and mode of administration:	• RGH-478 50 mg strength capsules; stable dosing at 50 mg 2 times a day (BID) (total RGH-478 dose 100 mg/day); oral administration after meals for 28 days.
Reference therapy, dose, and method of administration:	• Active comparator (Celecoxib): 100 mg strength capsules; stable dosing at 100 mg BID (total dose 200 mg/day); oral administration after meals for 28 days. • Matching placebo: 1 capsule BID; oral administration after meals for a duration of 28 days.
Main inclusion criteria:	Patients were to be included in the study only if they met all of the following criteria: 1) Male or female ≥ 40 years of age on the day of signing informed consent; 2) Diagnosis of OA of the knee for ≥ 6 months before signing informed consent according to American College of Rheumatology (ACR) criteria with X-ray confirmation of Kellgren-Lawrence grade 2 or 3 in the femoro-tibial compartment at screening and functional capacity class of I-III; 3) Pain of the index knee joint on more than 50% of days over the last month prior to screening requiring analgesic and/or anti-inflammatory treatment; 4) Currently receiving regular analgesics treatment (defined as drug intake for ≥ 4 days per week) for pain at the index knee joint. Analgesic treatment may include non-steroidal anti-inflammatory drugs ([NSAIDs] including cyclooxygenase-2 [COX-2] inhibitors), paracetamol, and/or weak opioids (e.g. tramadol) given at recommended dose ranges; 5) A Western Ontario & McMaster Universities Index of Osteoarthritis (WOMAC) VA3.1 pain visual analogue scale (VAS) score at Screening (Visit 1) ≥ 30 mm and ≤ 80 mm; 6) Willingness to abstain from use of NSAIDs (oral and topical other than the one given as study drug), other topical pain therapies (e.g., capsaicin), corticosteroids (systemic and intra-articular), viscosupplementation, and other pharmacological pain treatments during the study; 7) Willingness to abstain from the use of the permitted rescue medication (paracetamol) for 24 hours prior to all study visits; 8) Female patients of childbearing potential must have a negative serum pregnancy test (serum beta human chorionic gonadotropin) at screening unless they are

	surgically sterile or have been post-menopausal for ≥ 1 year (12 consecutive months without menses); 9) Women of childbearing potential must use a medically acceptable means of birth control and agree to continue its use during the study and for at least 4 weeks after the last dose of study drug. Medically acceptable forms of birth control include oral contraceptives, injectable or implantable methods, intrauterine devices, tubal ligation (if performed > 1 year before screening), or double barrier contraception. Sexually active male patients should be surgically sterile or agree to use a medically acceptable means of birth control; 10) Able to understand and willing to sign the informed consent prior to screening evaluations and agree to the schedule of assessments. 11) A WOMAC VA3.1 pain VAS score at Baseline (Visit 2) ≥ 50 mm, with an increase of ≥ 10 mm from Screening; 12) A Patient's Global Assessment (PGA) of disease activity at Baseline of fair, poor, or very poor; and 13) Patients need to have a minimum of 2 daily pain assessments via IVRS during the Screening Period;
Main exclusion criteria	If the patients had met any of the following criteria they were excluded from the study: 1) Surgery, including arthroscopy, of the index knee joint within 3 months of screening or any scheduled surgery or painful procedure of the index knee joint during the course of the study; 2) Intra-articular corticosteroid to the index knee joint within 3 months prior to screening or to any other joint within 4 weeks prior to screening; 3) Hyaluronic acid intra-articular injection to the index knee joint within 6 months prior to screening; 4) Systemic corticosteroids (oral, intramuscular, or intravenous) within 4 weeks prior to screening; 5) Physical therapy and other non-pharmacological pain therapy (e.g. transcutaneous electrical nerve stimulation, acupuncture, and psychological support) unless dose was stable for ≥ 1 months prior to screening or planning the initiation of such therapy during the study; 6) Nutritional supplementation for OA (e.g. chondroitin sulfate, glucosamine, diacerein or avocado-soybean unsaponifiables (ASU) etc.) unless dose was stable for ≥ 1 months prior to screening or planning the initiation of such therapy during the study;

	7) Radiotherapy for chronic articular pain within 3 months prior to screening or planning the initiation of such therapy during the study; 8) Initiation of the use of medications for treating chronic pain (including anticonvulsants, tricyclic antidepressants, unselective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors etc.) within 2 weeks prior to screening or planning the initiation of any new anti-pain therapy or treatment during the study; 9) Initiation of the use of hypnotics or change in the dosing regimen of current hypnotics including benzodiazepines and non-benzodiazepine hypnotics within 2 weeks prior to screening; 10) Current use of anticoagulant drugs or antiaggregants (including low-dose acetylsalicylic acid); 11) Body mass index (BMI) < 18 or > 39 and/or body weight <40 kg at screening; 12) Clinically relevant history of hypersensitivity or allergy to study drug, celecoxib, or paracetamol or any of their excipients as well as existence of a medical condition or use of concomitant medication for which the use of celecoxib or paracetamol is contraindicated; 13) Known hypersensitivity to sulphonamides; 14) Had previously failed treatment with or showed intolerance to NSAIDs, including COX-2 inhibitors; 15) History of asthma, acute rhinitis, angioedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid, ibuprofen, or other NSAIDs, including COX-2 inhibitors; 16) Any medical conditions other than pain due to OA that could interfere with study evaluations, e.g., anatomical deformities, fibromyalgia, chronic pain syndrome or other arthritic conditions other than OA of the knee; 17) Known or clinically suspected infection with human immunodeficiency virus, hepatitis C or B viruses; 18) Congestive heart failure (New York Heart Association class II-IV); history of clinically significant cardiovascular disease including, but not limited to, myocardial infarction, unstable angina, peripheral arterial disease, and stroke or transient ischemic attack; uncontrolled hypertension (systolic blood pressure [BP] >160 mm Hg or diastolic BP >100 mm Hg) ; 19) Active or history of recurrent peptic ulcer/hemorrhage or gastrointestinal perforation; history of gastrointestinal bleeding, history of inflammatory bowel disease;

	20) History of congenital QTc prolongation or QTc duration at the screening electrocardiogram (ECG) ≥ 450 msec for men or ≥ 470 msec for women; 21) Severe renal or hepatic insufficiency; or serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2x upper limit of normal (ULN), serum gamma-glutamyl transpeptidase (GGT) > 3x ULN, serum albumin < 2.5 g/dL, serum bilirubin > ULN, or estimated serum creatinine clearance ≤ 30 mL/minute at screening; 22) Any clinically significant condition or laboratory result that in the Investigator's judgment may affect efficacy or safety assessments or may compromise the patient's safety during study participation, including but not limited to, cardiopulmonary, metabolic, gastrointestinal, hematologic, or psychiatric disorders; 23) History of malignancy within the past 5 years (except for basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been treated with no evidence of recurrence); 24) Participation in any investigational drug/device clinical study or in biological agent clinical studies within 3 months prior to screening; 25) History within the previous 2 years or current evidence of drug or alcohol abuse; 26) Pregnant or lactating women; and 27) Any condition or circumstances which in the opinion of the Investigator may make a patient unlikely or unable to complete the study or comply with study procedures and requirements, or may pose a risk to the patient's safety.
Endpoints:	**Primary Efficacy:** The primary efficacy endpoint was the change from baseline to V5 (Week 4) in the WOMAC VA3.1 pain VAS subscale. **Secondary Efficacy:** The secondary efficacy endpoints included: • Change from baseline at V3 (Week 1), V4 (Week 2), and V5 (Week 4) in the average daily pain intensity score evaluated on a Numeric Rating Scale (NRS); • WOMAC VA3.1 Pain VAS subscale change from baseline at V3 (Week 1) and V4 (Week 2); • WOMAC VA3.1 Stiffness subscale change from baseline at V3 (Week 1), V4 (Week 2), and V5 (Week 4);

	• WOMAC VA3.1 Physical function subscale change from baseline at V3 (Week 1), V4 (Week 2), and V5 (Week 4); • WOMAC VA3.1 Global Score change from baseline at V3 (Week 1), V4 (Week 2), and V5 (Week 4); • Changes from baseline in PGA of disease activity scores at V3 (Week 1), V4 (Week 2), and V5 (Week 4); • Percent of responders according to OMERACT-OARSI criteria at V3 (Week 1), V4 (Week 2), and V5 (Week 4); • Use of rescue medication; and • Exploratory evaluation of selected biomarkers of inflammation and joint/cartilage damage.
Safety parameters:	• Adverse events; • Vital signs (supine heart rate and blood pressure [systolic and diastolic]); • Physical examination; • 12-lead ECG; and • Clinical laboratory tests (hematology, blood chemistry, and urinalysis).
Statistical methods:	All tables, statistical analyses, figures, and patient data listings were generated using SAS® Version 9.1.3. Data summaries were presented by treatment group. Continuous variables were summarized using summary statistics (number of patients [N], mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized using frequency counts and percentages. No formal hypothesis testing was performed on the demographic and baseline characteristic data for this study. All safety data were summarized for the safety population. No formal statistical comparisons of safety data were performed. Inferential treatment comparisons were declared statistically significant at the 5% level using 2-tailed tests. RGH-478 was compared with Placebo in the statistical analyses. For estimation of treatment effects, 95% confidence intervals were presented for the mean changes from baseline for each treatment group and for the difference in means between the treatment groups. Since this was an exploratory study, no adjustment for multiple testing of secondary efficacy endpoints was performed. The efficacy analyses were intended to

	provide guidance for the design of future Phase II and III studies. Baseline values for both safety and efficacy analyses were defined as the last observation prior to dosing. For patients who discontinue from the study, efficacy assessments were imputed using methods such as last observation carried forward or baseline observation carried forward. An interim analysis was not planned.
Analysis sets:	Safety population: 244 Intention to treat population: 235 Per protocol population: 180
Results:	The primary objective of the study was to preliminarily evaluate the efficacy of RGH-478 compared with placebo in patients with OA, while the secondary objectives of this study were to assess the safety and tolerability of RGH-478 in patients with OA. Altogether 25 sites were opened, of which 17 sites screened altogether 328 patients in Hungary. Of the screened patients altogether 248 patients were enrolled. 4 patients did not receive any IMP. 180 patients completed the study per protocol; 25 patients were withdrawn or dropped out from the study prematurely (9 patient from the RGH-478 group, 11 from the Placebo group, 5 from the Celecoxib group). With regards to the primary efficacy parameter, WOMAC VA3.1 mean pain score there was no statistically significant difference detected between RGH-478 and placebo using t-test for ITT and PP population. No statistically significant difference was found between treatments using the repeated measures ANCOVA model for WOMAC VA3.1 mean pain score for ITT and PP population, either. Regarding the secondary target parameters there were scattered differences that were statistically significant: • Daily pain intensity score at Visit 3 as compared to baseline between placebo and Celecoxib in both the ITT and PP populations (P=0.0317 and P=0.0345, respectively). • PGA of disease activity score between RGH-478 and Celecoxib at visit 4 (p-value: 0.0320). • Percent of responders according to OMERACT-OARSI criteria between RGH-478 and Celecoxib (P=0.0189) and between RGH-478 and Placebo (P=0.0377) for ITT population and between RGH-478 and Placebo (P=0.0260) for PP population at visit 4.

	• In the use of rescue medication between Celecoxib and placebo group in the ITT population (P=0.0086). Detailed safety measures were observed during the study. Analysis of safety data proved all study IMPs to be safe and well-tolerated. No death or life-threatening adverse events occurred. One SAE was reported in the Celecoxib group, the reported term was worsening of diabetes mellitus, the patient was not withdrawn from the study, completed the clinical trial per protocol. The case was serious due to hospitalization, causality was assessed as not related by both the investigator and the sponsor.
Conclusion:	In summary it can be concluded that the changes observed in the primary and secondary efficacy parameters are insufficient to support the study hypothesis in this population of OA patients. Further studies may be needed in other patient populations/indications to further evaluate biological efficaciousness of RGH-478.