

EudraCT: 2018-004730-15  
IND: 141725

Regeneron Pharmaceuticals, Inc.

**Clinical Study Protocol****A RANDOMIZED, DOUBLE-BLIND, MULTI-DOSE,  
PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY  
AND SAFETY OF REGN5069 IN PATIENTS WITH PAIN DUE TO  
OSTEOARTHRITIS OF THE KNEE**

**Compound:** REGN5069

**Clinical Phase:** 2

**Protocol Number:** R5069-OA-1849

**Protocol Version:** R5069-OA-1849 Amendment 1

**Amendment 1 Date of Issue:** *See appended electronic signature page*

**Original Date of Issue:** 30 Jan 2019

**Medical/Study Director:**

[REDACTED] Early Clinical  
Development and Experimental Sciences  
Regeneron Pharmaceuticals, Inc.  
777 Old Saw Mill River Road  
Tarrytown, NY 10591



## AMENDMENT HISTORY

### *Amendment 1*

The purpose of this amendment is to add an end-of-study phone call to collect long-term information on patient status regarding joint replacement surgery beyond the current planned follow-up period, per health authority feedback, and to extend the required duration for serious adverse event (SAE) reporting, pregnancy reporting, and the use of contraceptive measures. Changes were also made to the statistical analysis plan based on health authority feedback. The following table outlines the changes made to the protocol and the rationale.

| Change and Rationale   | Sections Changed   |
|--|--|
| <p>An end-of-study phone call will be conducted approximately 52 weeks after the first dose of study drug to collect long-term information on patient status regarding joint replacement surgery (ie, whether the patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer). This change was made per health authority feedback.</p> <p>As a result of this change, the study duration, end of study definition, and any prior reference to the “end of study” that now refers to the “end of the follow-up period” were updated for accuracy.</p> | <p><a href="#">Clinical Study Protocol Synopsis</a>: Study Design; Study Duration; End of Study Definition; Procedures and Assessments</p> <p>Section 3.2.1 Rationale for Study Design</p> <p>Section 5.1 Study Description and Duration</p> <p><a href="#">Figure 1</a>: Study Flow Diagram</p> <p>Section 5.1.2 End of Study Definition</p> <p>Section 7.3.2 Study Drug Discontinuation</p> <p>Section 7.7 Concomitant Medications and Procedures</p> <p>Section 7.7.1 Prohibited Medications and Procedures</p> <p>Section 7.7.2 Permitted Medications and Procedures</p> <p><a href="#">Table 1</a>: Schedule of Events</p> <p>Section 8.1.1 Footnotes for the Schedule of Events Table 1, #10</p> <p>Section 8.1.2 Footnotes for Schedule of Events for Follow-up of Patients Who Undergo Joint Replacement Surgery (Table 2)</p> <p>Section 8.2.3.8 End-of-Study Phone Call for Joint Replacement Status Questionnaire (added section)</p> <p>Section 9.4.1 Adverse Events</p> <p>Section 9.4.2 Serious Adverse Events</p> |
| <p>The required duration for pregnancy reporting and the use of contraceptive measures for sexually active men and women of childbearing potential was extended from 7 months to at least 9 months after the last dose of study drug. The duration for SAE reporting in the event that the investigator is informed of an SAE after a patient terminates early from the study was increased from onset of the SAE “within 169 days of last study drug administration” to “within 226 days of last study drug administration.” These changes were based on recently analyzed clinical pharmacology data from the ongoing first-in-human study R5069-HV-1810.</p>            | <p>Section 6.2.2 Exclusion Criteria, #28 and #31</p> <p>Section 9.4.2 Serious Adverse Events</p> <p>Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor</p>   |

|  |   |
|--|---|
| Details on the planned analyses of X-ray and magnetic resonance imaging data were added, per health authority feedback.  | Section 8.2.3.6 Imaging<br>Section 10.4.4.2 Other Safety, added “Imaging” in this analysis subsection   |
| The primary efficacy analysis plan was updated to reflect that change from baseline to week 12 in the Western Ontario and McMaster Osteoarthritis Index pain subscale will be a multiple imputation approach with analysis of covariance (ANCOVA) based on the full analysis set with adjustment for missing data using a pattern mixture approach. Additionally, information was provided regarding the plan for handling missing data. These changes were made per health authority feedback.                        | <a href="#">Clinical Study Protocol Synopsis</a> : Statistical Plan, Primary Efficacy Analysis<br>Section 10.4.3.1 Primary Efficacy Analysis  |
| The protocol language was modified to remove flexibility for dosing of REGN5069. Previously, the low dose of REGN5069 was estimated to be 100 mg IV every 4 weeks (Q4W) and the high dose of REGN5069 was estimated to be 1000 mg IV Q4W. Flexibility was built in such that the high dose may have been adjusted downward and such that the low dose may have been adjusted downward or upward. The REGN5069 100 mg IV Q4W and REGN5069 1000 mg IV Q4W doses are the 2 doses that will be administered in this study. | <a href="#">Clinical Study Protocol Synopsis</a> : Study Design<br>Section 3.2.2 Rationale for Dose Selection<br>Section 5.1 Study Description and Duration<br>Section 7.1 Investigational Treatments<br>Section 7.5 Method of Treatment Assignment |
| Genicular nerve block and any similar procedures are now listed as prohibited within 3 months of the screening visit to qualify for study participation and are prohibited up to the last study site visit in the follow-up period. Use of such procedures may interfere with pain perception.   | Section 6.2.2 Exclusion Criteria, #32 (added)<br>Section 7.7.1 Prohibited Medications and Procedures  |
| The section entitled “Reasons for Temporary Discontinuation of Study Drug” was removed, as any discontinuation from study drug dosing will be permanent.   | Section 7.3.2.2 Reasons for Temporary Discontinuation of Study Drug (deleted section)<br>Section 6.3 Premature Withdrawal from the Study  |
| To provide guidance to study sites, language was added to state that patients with a history of hypothyroidism must have thyroid-stimulating hormone levels measured and must be in an euthyroid state to be eligible for study participation.   | Section 6.2.2 Exclusion Criteria, #1  |
| The specific value for follicle-stimulating hormone levels to fall in the postmenopausal range was removed for flexibility.  | Section 6.2.2 Exclusion Criteria, #31   |
| All drug and alcohol testing will be performed with urine samples which are sufficient for this test based on central laboratory feedback. Thus, any serum sample collection previously specified for drug and alcohol testing was changed to urine sample collection and instructions in the event of a positive drug and/or alcohol test result were updated.  | Section 8.1 Schedule of Events, <a href="#">Table 1</a><br>Schedule of Events<br>Section 8.1.1 Footnotes for the Schedule of Events Table 1, #11<br>Section 8.2.3.10 Laboratory Testing   |
| Specific statements regarding where laboratory samples will be processed were removed to allow flexibility.  | Section 8.2.3.10 Laboratory Testing   |
| Updated information regarding the first-in-human study R5069-HV-1810 based on the current status of the study.   | Section 1.1 Background<br>Section 3.2.1 Rationale for Study Design<br>Section 3.2.2 Rationale for Dose Selection  |
| Removed reference to “study reference manual,” as there is no study reference manual.  | Throughout the protocol.  |

|   |   |
|---|---|
| Minor edits were made to improve clarity throughout the protocol. | <p><a href="#">Clinical Study Protocol Synopsis: Statistical Plan, Justification of the Sample Size</a></p> <p><a href="#">List of Abbreviations and Definitions of Terms</a></p> <p>Section <a href="#">6.2.1</a> Inclusion Criteria, #12</p> <p>Section <a href="#">6.2.2</a> Exclusion Criteria, #21, 23, 24</p> <p><a href="#">Table 1: Schedule of Events</a></p> <p>Section <a href="#">8.1.3</a> Early Termination Visit</p> <p>Section <a href="#">8.2.6.1</a> Pharmacodynamic and Biomarker Research</p> <p>[REDACTED]</p> <p>Section <a href="#">9.3.2</a> Serious Adverse Event</p> <p>Section <a href="#">10.2</a> Justification of Sample Size</p> |
|---|---|

## CLINICAL STUDY PROTOCOL SYNOPSIS

|                                  |  |
|----------------------------------|--|
| <b>Title</b>                     | A Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Efficacy and Safety of REGN5069 in Patients with Pain due to Osteoarthritis of the Knee   |
| <b>Site Locations</b>            | Multiple sites in the United States (US) and ex-US   |
| <b>Principal Investigator(s)</b> | To be determined after 50% patient enrollment is completed   |
| <b>Objectives</b>                | <p><b>Primary Objective</b></p> <p>The primary objective of the study is to evaluate the efficacy of REGN5069 compared to placebo in patients with pain due to radiographically-confirmed osteoarthritis (OA) of the knee who have a history of inadequate joint pain relief or intolerance to current analgesic therapy.</p> <p><b>Secondary Objectives</b></p> <p>The secondary objectives of the study are:</p> <ul style="list-style-type: none"><li>• To characterize the concentrations of functional REGN5069 in serum over time when patients are treated for up to 12 weeks</li><li>• To assess the safety and tolerability of REGN5069 compared with placebo when patients are treated for up to 12 weeks</li><li>• To measure levels of anti-drug antibodies (ADAs) against REGN5069 following multiple intravenous (IV) administrations</li></ul>  |
| <b>Study Design</b>              | This multicenter phase 2 study consists of a screening period of up to 30 days, followed by a 12-week randomized, double-blind, parallel-arm, placebo-controlled treatment period, a 24-week follow-up period, and an end-of-study phone call approximately 52 weeks after the first dose of study drug. The purpose of the end-of-study phone call is to determine whether a patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer. Up to approximately 240 patients will be randomized in a 1:1:1 ratio to receive a low dose of REGN5069 at 100 mg IV every 4 weeks (Q4W), and a high dose of REGN5069 at 1000 mg IV Q4W, or matching placebo Q4W. The index knee joint is defined as the knee joint affected by OA and selected for primary assessment for this study. Randomization will be stratified by Kellgren-Lawrence (K-L) category (2-3 vs 4) of the index knee joint at the screening visit and participation in the Moticon sub-study (yes vs no). |
| <b>Study Duration</b>            | Each patient will be enrolled in the study for approximately 56 weeks, including the screening period and the period up to the end-of-study phone call.  |
| <b>End of Study Definition</b>   | The end of study is defined as the date when the last patient completes the last phone call, withdraws from the study, or is lost to follow-up (ie, the patient can no longer be contacted by the investigator).   |

---

**Population**

**Sample Size:** Up to approximately 240 patients are planned for enrollment in this study.

**Target Population:** Men and women who are at least 40 years of age at the time of study entry with a clinical diagnosis of OA of the knee based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score  $\geq 2$ ) at the index knee joint.

---

**Treatments**

**Study Drug** REGN5069 or matching placebo.

**Dose/Route/Schedule:** 100 mg IV Q4W or 1000 mg IV Q4W or Placebo IV Q4W

**Rescue Treatment** Starting at the screening visit until after the week-24 study visit is completed, acetaminophen is the only study-permitted rescue medication. Acetaminophen tablets of selected brand and strength will be provided to patients by the study site for use as rescue medication for breakthrough OA pain. In advance of initiating the study, each study site must consult with the sponsor and select the brand and the strength of acetaminophen tablets that will be dispensed to patients as rescue medication. In the event that pain relief for OA pain is inadequate, patients will take acetaminophen, as needed, in accordance with the instructions provided with the medication by each study site, with a maximum of 3000 mg/day. The use of rescue medication is not allowed for 48 hours prior to the start of or during a scheduled study visit to minimize the confounding effects of rescue medication on efficacy measures.

---

**Endpoints**

**Primary:** The primary endpoint of the study is the change from baseline to week 12 in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale score in patients treated with REGN5069 compared to patients treated with placebo.

**Secondary:** The secondary efficacy endpoints of the study are:

- Change from baseline to week 12 in the WOMAC total score (based on the full survey) in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in the WOMAC physical function subscale score in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in the Patient Global Assessment score in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in WOMAC stiffness subscale score in patients treated with REGN5069 compared to patients treated with placebo
- Percentage of patients treated with REGN5069, compared to that of patients treated with placebo, who had a response at week 12, with response defined as an improvement by  $\geq 30\%$  in

---

the WOMAC pain subscale scores

The secondary safety endpoints of the study are:

- The incidence of treatment-emergent adverse events in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration
- The incidence of imaging abnormalities consistent with accelerated arthropathies as assessed by X-ray and magnetic resonance imaging in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration
- Presence of anti-REGN5069 antibody development in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration

---

**Procedures and Assessments****Efficacy**

Efficacy will be assessed through administration of the WOMAC full survey and subsections of the survey, and through administration of the Patient Global Assessment of OA.

**Safety**

Safety procedures include monitoring vital signs, orthostatic vital sign change, physical and neurological examinations, electrocardiograms, joint imaging, a joint pain questionnaire, drug concentration and ADA sample collections, and additional laboratory testing. An end-of-study phone call will be conducted approximately 52 weeks after the first dose of study drug to collect long-term information on patient status regarding joint replacement surgery (ie, whether the patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer).

---

**Statistical Plan****Statistical Hypotheses**

The null hypotheses of no treatment difference between a REGN5069 dose and placebo against an alternative hypothesis of some treatment difference in change from baseline to week 12 in WOMAC pain subscale, physical function subscale, and Patient Global Assessment scores will be tested for each dose. Multiplicity adjustment for the 6 null hypotheses will be made using sequentially rejective multiple test procedure to control Type I error rate at 2-sided 0.05 level in the following order:

- H1: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC pain subscale score
- H2: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC pain subscale score
- H3: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC physical function subscale score
- H4: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC physical function subscale score

---

---

- H5: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in Patient Global Assessment score
- H6: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in Patient Global Assessment score

If at any step a null hypothesis is not rejected, the testing will stop and no further hypothesis in the order will be tested. Further details will be provided in the Statistical Analysis Plan.

#### **Justification of the Sample Size**

Up to approximately 240 patients (80 per treatment group) will be randomized to 3 treatment groups in a 1:1:1 allocation. Assuming a standard deviation of 2.3, 80 patients per treatment group will provide approximately 80% power to detect a treatment difference of 1.1 between the REGN5069 dose and matching placebo in change from baseline to week 12 in WOMAC pain subscale (using a significance level of 0.05, 2-sided t-test and assuming a dropout rate of 15% [6% due to lack of efficacy or adverse events, and 9% due to other reasons]).

#### **Primary Efficacy Analysis**

The primary estimand for the primary objective is the difference in means between both REGN5069 dose + protocol-defined rescue medication and placebo + protocol-defined rescue medication in the change from baseline to week 12 in the WOMAC pain subscale score of patients in the FAS. All collected data will be included in the analysis regardless of whether prohibited medication was taken. Missing values will be imputed with the multiple imputation approach, where intermediate missing data will be first imputed using the Markov Chain Monte Carlo method and then the remaining missing data with a monotone missing pattern will be imputed with a regression method. The regression model will adjust for treatment, randomization strata, and baseline score. For patients who drop out due to lack of efficacy or adverse events, each imputed value will be further adjusted by subtracting the mean change from baseline to the respective post-baseline time point calculated from patients in the same treatment group with observed data at that time point. For each complete dataset, the primary efficacy endpoint of change from baseline to week 12 in WOMAC pain subscale score will be analyzed using an analysis of covariance (ANCOVA) model which will include treatment, randomization strata, and baseline score as covariate. The least-squares means estimates as well as the difference of the estimates between each dose and placebo with standard error, p-values, and 95% confidence intervals will be provided by combining results from the analyses of the multiple imputed datasets using Rubin's formulae. Further details will be provided in the statistical analysis plan.

#### **Secondary Efficacy Analysis**

The continuous secondary endpoints will be analyzed similarly to the primary endpoint. For the analyses of categorical secondary endpoints, the Cochran-Mantel-Haenszel test stratified by the K-L category (2-3 vs 4) will be used with missing data considered as non-response.

---

**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

|                     |  |
|---------------------|--|
| Acetaminophen       | The United States Adopted Name for the International Nonproprietary Name paracetamol. Acetaminophen is the term used throughout this protocol. |
| ADA                 | Anti-drug antibody   |
| AE                  | Adverse event  |
| AESI                | Adverse event of special interest  |
| ALT                 | Alanine aminotransferase   |
| ANCOVA              | Analysis of covariance   |
| AST                 | Aspartate aminotransferase   |
| AUC                 | Area under the curve   |
| Bpm                 | Beats per minute   |
| CFA                 | Complete Freund's adjuvant   |
| CGRP                | Calcitonin gene-related peptide  |
| CPK                 | Creatine phosphokinase   |
| CRF                 | Case report form (electronic or paper)   |
| CRO                 | Contract research organization   |
| C <sub>trough</sub> | Trough concentration   |
| EC                  | Ethics Committee   |
| ECG                 | Electrocardiogram  |
| EDC                 | Electronic data capture  |
| ESR                 | Erythrocyte sedimentation rate   |
| EU                  | European Union   |
| FAS                 | Full analysis set  |
| FIH                 | First-in-human   |
| FSH                 | Follicle-stimulating hormone   |
| GCP                 | Good Clinical Practice   |
| GDNF                | Glial cell-line-derived neurotrophic factor  |
| GFR $\alpha$ 3      | Glial cell-line-derived neurotrophic factor receptor alpha-3   |
| HbA1c               | Hemoglobin A1c; Glycated hemoglobin  |
| HIV                 | Human immunodeficiency virus   |
| hsCRP               | High sensitivity C-reactive protein  |
| HV                  | Healthy volunteer  |
| ICF                 | Informed consent form  |
| ICH                 | International Council for Harmonisation  |
| Index knee joint    | The knee joint affected by osteoarthritis and selected for primary assessment  |

|           |   |
|-----------|---|
| INN       | International Nonproprietary Name                                 |
| IV        | Intravenous   |
| IWRS      | Interactive Web Response System                                   |
| K-L       | Kellgren-Lawrence   |
| MedDRA    | Medical Dictionary for Regulatory Activities                      |
| MRI       | Magnetic resonance imaging  |
| NGF       | Neuronal growth factor  |
| NOAEL     | No-observed-adverse-effect level                                  |
| NSAID     | Non-steroidal anti-inflammatory drug                              |
| OA        | Osteoarthritis  |
| PCSV      | Potentially clinically significant value                          |
| PD        | Pharmacodynamic   |
| PK        | Pharmacokinetic   |
| PPS       | Per protocol set  |
| PT        | Preferred term  |
| Q4W       | Every 4 weeks   |
| QRS       | Complex of Q, R, and S waves on an electrocardiogram              |
| RBC       | Red blood cell  |
| Regeneron | Regeneron Pharmaceuticals, Inc.                                   |
| RET       | Receptor tyrosine kinase  |
| SAE       | Serious adverse event   |
| SAF       | Safety analysis set   |
| SAP       | Statistical analysis plan   |
| SAS       | Statistical Analysis System                                       |
| SC        | Subcutaneous  |
| SD        | Standard deviation  |
| SOC       | System organ class  |
| SUSAR     | Suspected unexpected serious adverse reaction                     |
| TEAE      | Treatment-emergent adverse event                                  |
| TrkA      | Tropomyosin receptor kinase A                                     |
| TRPV1     | Transient receptor potential caption channel subfamily V member 1 |
| ULN       | Upper limit of normal   |
| US        | United States   |
| vs        | Versus  |
| WBC       | White blood cell  |
| WOCBP     | Women of childbearing potential                                   |
| WOMAC     | Western Ontario and McMaster Osteoarthritis Index                 |

**TABLE OF CONTENTS**

|   |    |
|---|----|
| AMENDMENT HISTORY .....                             | 2  |
| CLINICAL STUDY PROTOCOL SYNOPSIS.....               | 5  |
| LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS..... | 9  |
| 1. INTRODUCTION .....                               | 17 |
| 1.1. Background.....                                | 17 |
| 2. STUDY OBJECTIVES .....                           | 19 |
| 2.1. Primary Objective.....                         | 19 |
| 2.2. Secondary Objectives .....                     | 19 |
| 2.3. Exploratory Objectives .....                   | 19 |
| 3. HYPOTHESIS AND RATIONALE .....                   | 20 |
| 3.1. Hypothesis .....                               | 20 |
| 3.2. Rationale .....                                | 20 |
| 3.2.1. Rationale for Study Design.....              | 20 |
| 3.2.2. Rationale for Dose Selection .....           | 21 |
| 3.3. Risk-Benefit.....                              | 22 |
| 4. STUDY ENDPOINTS AND VARIABLES.....               | 22 |
| 4.1. Primary and Secondary Endpoints.....           | 22 |
| 4.1.1. Primary Endpoint.....                        | 22 |
| 4.1.2. Secondary Endpoints .....                    | 22 |
| 4.1.2.1. Secondary Efficacy Endpoints.....          | 22 |
| 4.1.2.2. Secondary Safety Endpoints .....           | 22 |
| 4.1.3. Exploratory Endpoints .....                  | 23 |
| 4.2. Demographic and Baseline Characteristics ..... | 23 |
| 4.3. Pharmacokinetic Variables .....                | 23 |
| 4.4. Immunogenicity Variables.....                  | 23 |
| 5. STUDY DESIGN .....                               | 24 |
| 5.1. Study Description and Duration .....           | 24 |
| 5.1.1. Study Stopping Rules .....                   | 24 |
| 5.1.2. End of Study Definition.....                 | 25 |
| 5.2. Planned Interim Analysis.....                  | 25 |
| 5.3. Study Committees.....                          | 25 |

|          |   |    |
|----------|---|----|
| 5.3.1.   | Independent Data Monitoring Committee .....                       | 25 |
| 6.       | SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS .....          | 25 |
| 6.1.     | Number of Patients Planned .....                                  | 25 |
| 6.2.     | Study Population.....   | 25 |
| 6.2.1.   | Inclusion Criteria .....  | 25 |
| 6.2.2.   | Exclusion Criteria .....  | 26 |
| 6.3.     | Premature Withdrawal from the Study .....                         | 30 |
| 6.4.     | Replacement of Patients .....                                     | 30 |
| 7.       | STUDY TREATMENTS.....   | 30 |
| 7.1.     | Investigational Treatments.....                                   | 30 |
| 7.2.     | Rescue Treatment .....  | 30 |
| 7.3.     | Dose Modification and Study Treatment Discontinuation Rules ..... | 31 |
| 7.3.1.   | Dose Modification .....   | 31 |
| 7.3.2.   | Study Drug Discontinuation .....                                  | 31 |
| 7.3.2.1. | Reasons for Permanent Discontinuation of Study Drug.....          | 31 |
| 7.4.     | Management of Acute Reactions.....                                | 31 |
| 7.4.1.   | Acute Intravenous Infusion Reactions.....                         | 31 |
| 7.4.1.1. | Interruption of the Intravenous Infusion .....                    | 31 |
| 7.4.1.2. | Termination of the Intravenous Infusion .....                     | 32 |
| 7.5.     | Method of Treatment Assignment .....                              | 33 |
| 7.5.1.   | Blinding .....  | 33 |
| 7.5.2.   | Emergency Unblinding.....   | 33 |
| 7.6.     | Treatment Logistics and Accountability.....                       | 34 |
| 7.6.1.   | Packaging, Labeling, and Storage .....                            | 34 |
| 7.6.2.   | Supply and Disposition of Treatments .....                        | 34 |
| 7.6.3.   | Treatment Accountability .....                                    | 34 |
| 7.6.4.   | Treatment Compliance.....   | 34 |
| 7.7.     | Concomitant Medications and Procedures .....                      | 34 |
| 7.7.1.   | Prohibited Medications and Procedures .....                       | 35 |
| 7.7.2.   | Permitted Medications and Procedures .....                        | 35 |
| 8.       | STUDY SCHEDULE OF EVENTS AND PROCEDURES .....                     | 36 |
| 8.1.     | Schedule of Events .....  | 36 |
| 8.1.1.   | Footnotes for the Schedule of Events Table 1 .....                | 40 |

|           |   |    |
|-----------|---|----|
| 8.1.2.    | Footnotes for Schedule of Events for Follow-up Period of Patients Who Undergo Joint Replacement Surgery (Table 2) ..... | 42 |
| 8.1.3.    | Early Termination Visit .....   | 42 |
| 8.1.4.    | Unscheduled Visits .....  | 42 |
| 8.2.      | Study Procedures .....  | 43 |
| 8.2.1.    | Procedures Performed at the Screening/Baseline Visit .....  | 43 |
| 8.2.1.1.  | Determination of Osteoarthritis of the Knee .....   | 43 |
| 8.2.1.2.  | Height .....  | 43 |
| 8.2.1.3.  | Weight.....   | 43 |
| 8.2.2.    | Efficacy Procedures .....   | 44 |
| 8.2.2.1.  | Western Ontario and McMaster Osteoarthritis Index.....  | 44 |
| 8.2.2.2.  | Patient Global Assessment of Osteoarthritis .....   | 44 |
| 8.2.3.    | Safety Procedures .....   | 44 |
| 8.2.3.1.  | Vital Signs .....   | 44 |
| 8.2.3.2.  | Orthostatic Vital Sign Assessment .....   | 44 |
| 8.2.3.3.  | Physical Examination with Joint Exam .....  | 45 |
| 8.2.3.4.  | Electrocardiogram.....  | 45 |
| 8.2.3.5.  | Neurological Examination .....  | 45 |
| 8.2.3.6.  | Imaging .....   | 45 |
| 8.2.3.7.  | Joint Pain Questionnaire .....  | 46 |
| 8.2.3.8.  | End-of-Study Phone Call for Joint Replacement Status Questionnaire .....  | 46 |
| 8.2.3.9.  | Knee Society Score for Joint Replacement Follow-up Only.....  | 46 |
| 8.2.3.10. | Laboratory Testing.....   | 46 |
| 8.2.4.    | Drug Concentration and Measurements .....   | 48 |
| 8.2.5.    | Anti-Drug Antibody Measurements and Samples.....  | 48 |
| 8.2.6.    | Biomarker, Pharmacodynamic, [REDACTED] and Other Research.....  | 48 |
| 8.2.6.1.  | Pharmacodynamic and Biomarker Research .....  | 48 |
| 8.2.6.2.  | [REDACTED]  |    |
| 8.2.6.3.  | [REDACTED]  |    |
| 8.2.6.4.  | Collection of Arthroplasty Tissue Samples (Joint Replacement Surgery Only) .....  | 49 |
| 8.2.6.5.  | Histological Evaluation of Tissue Samples (Joint Replacement Surgery Only) .....  | 49 |

|          |   |    |
|----------|---|----|
| 8.2.6.6. | Moticon Digital Insole Device Sub-Study for Gait Assessments.....   | 49 |
| 9.       | SAFETY DEFINITIONS, REPORTING, AND MONITORING .....                 | 50 |
| 9.1.     | Obligations of Investigator .....                                   | 50 |
| 9.2.     | Obligations of Sponsor .....  | 50 |
| 9.3.     | Definitions .....   | 50 |
| 9.3.1.   | Adverse Event.....  | 50 |
| 9.3.2.   | Serious Adverse Event.....  | 51 |
| 9.3.3.   | Adverse Events of Special Interest .....                            | 51 |
| 9.3.4.   | Infusion Reactions .....  | 51 |
| 9.4.     | Recording and Reporting Adverse Events.....                         | 52 |
| 9.4.1.   | Adverse Events .....  | 52 |
| 9.4.2.   | Serious Adverse Events .....  | 52 |
| 9.4.3.   | Other Events that Require Accelerated Reporting to Sponsor .....    | 52 |
| 9.4.4.   | Reporting Adverse Events Leading to Withdrawal from the Study ..... | 53 |
| 9.4.5.   | Abnormal Laboratory, Vital Signs, or Electrocardiogram Results..... | 53 |
| 9.4.6.   | Follow-up.....  | 53 |
| 9.5.     | Evaluation of Severity and Causality .....                          | 53 |
| 9.5.1.   | Evaluation of Severity .....  | 53 |
| 9.5.2.   | Evaluation of Causality.....  | 54 |
| 9.6.     | Safety Monitoring.....  | 56 |
| 9.7.     | Investigator Alert Notification.....                                | 56 |
| 10.      | STATISTICAL PLAN.....   | 56 |
| 10.1.    | Statistical Hypothesis.....   | 56 |
| 10.2.    | Justification of Sample Size.....                                   | 57 |
| 10.3.    | Analysis Sets.....  | 57 |
| 10.3.1.  | Efficacy Analysis Sets .....  | 57 |
| 10.3.2.  | Safety Analysis Set .....   | 57 |
| 10.3.3.  | Per Protocol Set .....  | 57 |
| 10.3.4.  | Pharmacokinetic Analysis Sets.....                                  | 58 |
| 10.3.5.  | Anti-Drug Antibody Analysis Sets .....                              | 58 |
| 10.4.    | Statistical Methods.....  | 58 |
| 10.4.1.  | Patient Disposition.....  | 58 |
| 10.4.2.  | Demography and Baseline Characteristics .....                       | 58 |

|           |   |    |
|-----------|---|----|
| 10.4.3.   | Efficacy Analyses .....   | 58 |
| 10.4.3.1. | Primary Efficacy Analysis .....   | 58 |
| 10.4.3.2. | Secondary Efficacy Analysis .....   | 59 |
| 10.4.4.   | Safety Analysis .....   | 59 |
| 10.4.4.1. | Adverse Events .....  | 59 |
| 10.4.4.2. | Other Safety .....  | 60 |
| 10.4.4.3. | Treatment Exposure .....  | 60 |
| 10.4.4.4. | Treatment Compliance .....  | 61 |
| 10.4.5.   | Pharmacokinetics .....  | 61 |
| 10.4.5.1. | Analysis of Drug Concentration Data .....   | 61 |
| 10.4.5.2. | Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses .....             | 61 |
| 10.4.6.   | Analysis of Anti-Drug Antibody Data .....   | 61 |
| 10.5.     | Interim Analysis .....  | 61 |
| 10.6.     | Additional Statistical Data Handling Conventions .....                            | 62 |
| 10.7.     | Statistical Considerations Surrounding the Premature Termination of a Study ..... | 62 |
| 11.       | DATA MANAGEMENT AND ELECTRONIC SYSTEMS .....                                      | 62 |
| 11.1.     | Data Management .....   | 62 |
| 11.2.     | Electronic Systems .....  | 63 |
| 12.       | STUDY MONITORING .....  | 63 |
| 12.1.     | Monitoring of Study Sites .....   | 63 |
| 12.2.     | Source Document Requirements .....  | 63 |
| 12.3.     | Case Report Form Requirements .....   | 63 |
| 13.       | AUDITS AND INSPECTIONS .....  | 64 |
| 14.       | ETHICAL AND REGULATORY CONSIDERATIONS .....                                       | 64 |
| 14.1.     | Good Clinical Practice Statement .....  | 64 |
| 14.2.     | Informed Consent .....  | 64 |
| 14.3.     | Patients Confidentiality and Data Protection .....                                | 65 |
| 14.4.     | Institutional Review Board/Ethics Committee .....                                 | 65 |
| 14.5.     | Clinical Study Data Transparency .....  | 66 |
| 15.       | PROTOCOL AMENDMENTS .....   | 66 |
| 16.       | PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE .....                   | 66 |
| 16.1.     | Premature Termination of the Study .....  | 66 |

|       |   |    |
|-------|---|----|
| 16.2. | Close-out of a Site .....                         | 66 |
| 17.   | STUDY DOCUMENTATION .....                         | 67 |
| 17.1. | Certification of Accuracy of Data.....            | 67 |
| 17.2. | Retention of Records .....                        | 67 |
| 18.   | DATA QUALITY ASSURANCE.....                       | 67 |
| 19.   | CONFIDENTIALITY .....                             | 68 |
| 20.   | FINANCING AND INSURANCE.....                      | 68 |
| 21.   | PUBLICATION POLICY .....                          | 68 |
| 22.   | REFERENCES .....                                  | 68 |
| 23.   | INVESTIGATOR'S AGREEMENT.....                     | 71 |
|       | SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS ..... | 72 |

## LIST OF TABLES

|          |  |    |
|----------|--|----|
| Table 1: | Schedule of Events .....   | 37 |
| Table 2: | Schedule of Events for Follow-up Period of Patients Who Undergo Joint Replacement Surgery..... | 42 |

## LIST OF FIGURES

|           |                         |    |
|-----------|-------------------------|----|
| Figure 1: | Study Flow Diagram..... | 24 |
|-----------|-------------------------|----|

## 1. INTRODUCTION

### 1.1. Background

Osteoarthritis (OA) is the most prevalent joint disease and a leading source of chronic pain and disability within the United States (US) ([Murray, 2013](#)) and other developed nations ([Vos, 2012](#)). Across the European Union (EU) Member States, OA prevalence has been reported to vary from 2.8% in Romania to 18.3% in Hungary ([Network EMCsAI, 2012](#)). From 2013 to 2015 in the US, 49.6% of adults age 65 years and older reported having a diagnosis of OA, and the prevalence continues to rise ([Centers for Disease Control and Prevention](#)). As the world's population continues to age, it is estimated that degenerative joint disease disorders such as OA will impact at least 130 million individuals around the globe by the year 2050 ([Maiese, 2016](#)).

Knee OA accounts for over 80% of the disease total burden ([Vos, 2012](#)). Knee OA is estimated to affect at least 19% of American adults 45 years of age and older ([Lawrence, 2008](#)). Across Europe, a lifetime risk of knee OA is estimated to be 45% ([Kingsbury, 2014](#)). More than half of patients with symptomatic knee OA are younger than age 65 years and will live for at least 3 decades after the initial diagnosis, making the burden of knee OA particularly large ([Deshpande, 2016](#)).

A wide variety of interventions have been evaluated for the management of pain due to OA, including: 1) non-pharmacological modalities (eg, education, exercise, and provision of walking aids); 2) pharmacological treatments, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and other centrally-active drugs (such as antidepressants); and 3) intra-articular injections of glucocorticoid and hyaluronan preparations and surgical treatments. Surgical treatments alone include a variety of approaches, such as knee aspiration and joint lavage, as well as osteotomy, knee fusion, and total joint replacement ([Malfait, 2013](#)) ([Zhang, 2007](#)). However, with the exception of radical surgical interventions, such as total joint replacement, the majority of patients do not receive adequate pain relief either because these approaches have suboptimal efficacy and/or because their use is limited by tolerability and toxicity. Non-pharmacological approaches are less efficacious than pharmacological treatments ([Zhang, 2007](#)). Among surgical treatments, reliable standardized effect size has been calculated for arthroscopic lavage and debridement, which were found to be no more effective than placebo ([Zhang, 2007](#)). The limitations of currently available analgesic therapies include a variety of adverse effects associated with each available treatment. Use of acetaminophen carries a risk of hepatic toxicity and of serious allergic reactions. Use of NSAIDs is associated with gastrointestinal bleeding and ulceration, cardiovascular events, and renal toxicity. Opioid agents are characterized by central nervous system depression, nausea, vomiting, and potential for abuse. Inadequate pain relief has a profound impact on the quality of life for patients with an associated great cost to society, including healthcare costs and loss of productivity. With the increasing number of OA patients, there is a growing unmet medical need for additional treatment options with improved pain relief and fewer associated side-effects.

Glial cell-line-derived neurotrophic factor (GDNF) receptor alpha-3 (GFR $\alpha$ 3) is 1 of at least 4 members of the GDNF receptor alpha (GFR $\alpha$ ) family. These receptors are glycosylphosphatidylinositol-linked proteins expressed in the central and peripheral nervous systems and are involved in the sensitization of pain-sensing neurons known as nociceptors

(Naveilhan, 1998) (Worby, 1998) (Baloh, 1998a). Artemin, the only known ligand for GFR $\alpha$ 3 (Baloh, 1998b), is a member of the GDNF family of ligands, which also includes GDNF, neurturin, and persephin (Baudet, 2000). These secreted ligands signal through the single-pass membrane receptor tyrosine kinase (RET) by clustering it with a GFR $\alpha$  receptor (Durbec, 1996) (Jing, 1997) (Treanor, 1996) (Trupp, 1999). Functional specificity of RET signaling is achieved by the specific GDNF family member binding to its preferred GFR $\alpha$  receptor.

In adult humans, GFR $\alpha$ 3 receptors are localized to dorsal root, trigeminal and sympathetic ganglia, as well as peripheral nerves (Bespalov, 2007). GFR $\alpha$ 3 is also expressed in the gastrointestinal system, and in mice this expression has been localized to the myenteric plexus of both the small and large intestine (unpublished results). Artemin RNA expression is observed in epithelial cells and keratinocytes (Mabbott, 2013) (unpublished results). Low levels of artemin RNA expression have also been reported in adult normal human tissues such as prostate, pituitary, and brain. Increased artemin RNA expression is reported in disease states such as chronic pancreatitis (Ceyhan, 2007), burning mouth syndrome (Shinoda, 2015), and atopic dermatitis (Murota, 2012). In conditions of tissue insult, such as local inflammation or trauma, it is hypothesized that the GFR $\alpha$ 3-artemin signaling pathway is activated in small diameter sensory neurons (positive for RET, Tropomyosin receptor kinase A [TrkA], transient receptor potential cation channel subfamily V member 1 [TRPV1], and calcitonin gene-related peptide [CGRP] expression). This activation may in turn upregulate these pathways, leading to hyperalgesia or allodynia. In support of a role for GFR $\alpha$ 3 signaling during pain states, pre-clinical studies have demonstrated that both anti-mouse and anti-human GFR $\alpha$ 3 receptor antibodies induced significant reductions in tactile allodynia and thermal hyperalgesia in the peri-articular complete Freund's adjuvant (CFA) model of inflammatory joint pain. Both mouse and human anti-GFR $\alpha$ 3 receptor antibodies also reduced the level of tactile allodynia in the destabilization of the medial meniscus mouse model of knee OA. The preclinical findings suggest that modulating the GFR $\alpha$ 3 pathway may provide an analgesic effect in patients with chronic pain conditions, such as pain due to OA of the knee.

REGN5069 is a human IgG4 monoclonal antibody that binds GFR $\alpha$ 3 with subnanomolar affinity. Through its binding to the extracellular domain of GFR $\alpha$ 3, REGN5069 interferes with the interaction of GFR $\alpha$ 3 with RET and prevents GFR $\alpha$ 3-mediated RET signaling. REGN5069 was isolated from Regeneron Pharmaceuticals, Inc.'s (Regeneron's) VelocImmune® human antibody mouse platform (Macdonald, 2014) (Murphy, 2014) and contains a human light chain variable domain fused to a human kappa constant domain and a human heavy chain variable region fused to a human IgG4 constant domain. The IgG4 constant domain contains a serine to proline amino acid substitution (S228P, Eu numbering, designated IgG4P) in the hinge region that reconstructs the human IgG1 hinge sequence (CPPC) to promote stabilization of disulfide bonds between the 2 heavy chains (Yang, 2014).

A first-in-human (FIH) randomized, double-blind, placebo-controlled, single ascending dose study of safety, tolerability, and pharmacokinetics (PK) of REGN5069 is currently ongoing in healthy volunteers. The design includes 7 cohorts: 5 cohorts to receive REGN5069 via intravenous (IV) injection of 30 mg, 100 mg, 300 mg, 1000 mg, or 3000 mg, and 2 cohorts to receive 300 mg or 600 mg by subcutaneous (SC) injection. To date, at which point dosing has been completed in the FIH study, REGN5069 has been well tolerated and no serious or severe adverse events (AEs) have been reported.

To the best of the sponsor's knowledge, REGN5069 is the first-in-class antibody intervening in the GFR $\alpha$ 3 signaling pathway to be developed as a potential analgesic agent. This proof-of-concept study is designed to evaluate efficacy and safety of 2 IV doses of REGN5069 in male and female patients with chronic pain due to knee OA after 12 weeks of treatment. The higher dose regimen is selected to maintain REGN5069 serum concentrations in excess of those associated with efficacy in a mouse model of thermal hyperalgesia and/or those associated with saturation of target-mediated disposition in serum, for the duration of each dosing interval. A lower dose regimen, which is expected to provide adequate separation in exposure and effect, also will be evaluated.

Additional background information on REGN5069 and the development program may be found in the current version of the Investigator's Brochure.

## **2. STUDY OBJECTIVES**

### **2.1. Primary Objective**

The primary objective of the study is to evaluate the efficacy of REGN5069 compared to placebo in patients with pain due to radiographically-confirmed OA of the knee who have a history of inadequate joint pain relief or intolerance to current analgesic therapy.

### **2.2. Secondary Objectives**

The secondary objectives of the study are:

- To characterize the concentrations of functional REGN5069 in serum over time when patients are treated for up to 12 weeks
- To assess the safety and tolerability of REGN5069 compared with placebo when patients are treated for up to 12 weeks
- To measure levels of anti-drug antibodies (ADAs) against REGN5069 following multiple IV administrations

### **2.3. Exploratory Objectives**

The exploratory objectives of the study are:

- To evaluate the effect of REGN5069 on inflammation in patients compared to that of placebo
- To evaluate the use of a digital, wearable, insole device to assess gait parameters and functional mobility in patients with OA of the knee without an analgesic treatment and after administration of a potential analgesic treatment

### 3. HYPOTHESIS AND RATIONALE

#### 3.1. Hypothesis

Based on its mechanism of action, REGN5069 is expected to provide clinically meaningful pain relief as assessed by the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale score in patients with pain due to radiographically-confirmed OA of the knee.

#### 3.2. Rationale

##### 3.2.1. Rationale for Study Design

This randomized, double-blind, multi-dose, parallel-arm, placebo-controlled study is designed to evaluate the safety and efficacy of REGN5069 in patients with pain due to OA of the knee who have a history of inadequate pain relief from acetaminophen\* and a history of intolerance or inadequate pain relief from oral NSAIDs (eg, prescription NSAIDs or over the counter NSAIDs at or near prescription doses), and opioid therapy or unavailability of opioid therapy. This study will guide further clinical development of REGN5069.

No safety concerns related to inhibition of the GFR $\alpha$ 3 receptor have been identified either in the literature or in preclinical toxicology studies performed by the sponsor. Preliminary safety data from the FIH study, including the 3000 mg IV cohort in healthy subjects, indicate that REGN5069 is well tolerated and that the safety is adequate for continued development. At the same time, the present study is planned to be conducted in patients suffering from chronic pain due to knee OA, who are either intolerant to or whose pain is not adequately relieved by the currently available analgesic agents, including acetaminophen, NSAIDs, and opioids. In addition, all of these agents are associated with risks of significant adverse effects, including gastrointestinal bleeding, increased risk of cardiovascular events and kidney damage associated with long-standing use of NSAIDs, and nausea, constipation, cognitive deficits, and undesired behaviors such as abuse and addiction associated with chronic use of opiates. Therefore, the subset of OA patients eligible for this study represents a patient population with an unmet medical need in whom the high disease burden of painful knee OA and the available safety and tolerability information for REGN5069 indicate that it is appropriate to prospectively study the hypothesis that REGN5069 provides substantial benefit (ie, clinically meaningful relief of pain from knee OA) and has an acceptable safety profile. Rescue medication (acetaminophen) will be allowed for any patient with breakthrough pain.

The study design is based on similar studies in the therapeutic area of chronic pain relief. The WOMAC survey, from which the primary endpoint and many of the secondary efficacy endpoints will be assessed, is a validated measurement used to assess pain, stiffness, and daily functioning in patients with OA.

Studies investigating agents that block neuronal growth factor (NGF) in a patient population with chronic pain due to OA have identified safety concerns, especially adjudicated arthropathies. The mechanism for these effects remain unknown but some have postulated that the arthropathy is related, at least in part, to the analgesia. Other serious potential risks include those related to sympathetic blockade, including potential effects on blood pressure. Accordingly, rigorous, precautionary safety monitoring (Section 8.2.3), including regular X-ray and magnetic resonance imaging (MRI), a joint pain questionnaire, and physical examinations with a focus on joints,

neurological examinations, monitoring of orthostatic vital signs, and laboratory testing is implemented in this study. In addition, a prolonged safety follow-up period of 24 weeks (twice the duration of the treatment period) is included in this study. While at present, there is no evidence that safety concerns associated with anti-NGF agents are associated with blocking GFR $\alpha$ 3, this rigorous medical monitoring is implemented to identify and protect patients against such potential concerns. Additionally, an end-of-study phone call approximately 52 weeks after the first dose of study drug will be conducted to collect long-term information beyond the follow-up period regarding whether a patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer.

\* Note: The International Nonproprietary Name (INN) for acetaminophen is paracetamol. This protocol will use the US Adopted Name acetaminophen.

### 3.2.2. Rationale for Dose Selection

Two dose regimens are planned for evaluation in this study. The high dose, 1000 mg IV Q4W, aims to deliver concentrations of REGN5069 in serum expected to exceed those associated with efficacy in a mouse thermal hyperalgesia model and those associated with target saturation in serum, for the duration of each dosing interval. The goal for the low dose, 100 mg IV Q4W, is to probe the dose-response curve with a dose expected to have adequate separation in exposure from the high dose and have efficacy that is less than that associated with the high dose but still measurably greater than the control.

For the high dose regimen, the target serum concentration to be exceeded at the end of each dosing interval (trough concentration [ $C_{trough}$ ]) includes 80 mg/L, the mean  $C_{trough}$  for a dose with near maximal efficacy identified in a mouse artemin thermal hyperalgesia model, and the concentration of REGN5069 in serum associated with saturation of GFR $\alpha$ 3. The latter was estimated using the available human PK data from the R5069-HV-1810 FIH study (Clinical Pharmacology data memo 19 Mar 2019). Both pharmacokinetic and pharmacodynamic (PK/PD) data in mice and serum target saturation data in humans were considered since it is not currently known which is better correlated with efficacy in humans. As noted above, the high dose regimen is selected to maintain serum concentrations of REGN5069 above these target concentrations through the end of each dosing interval and to yield a cumulative area under the curve (AUC) for the entire treatment period less than that observed for the no-observed-adverse-effect level (NOAEL) dose of 50 mg/kg in the 13-week monkey toxicology study. Based on population PK simulations in a virtual population of 500 subjects, a 1000 mg IV Q4W dosing regimen is predicted to yield a serum  $C_{trough}$  increasing from ~100 mg/L at the end of the first dosing interval to ~200 mg/L at the end of the last dosing interval, and a cumulative AUC ~8-fold less than that observed for the 13-week monkey NOAEL.

For the low dose regimen, the target serum concentration to be exceeded at the end of each dosing interval is 3 mg/L, the estimated mean  $C_{trough}$  in serum for the minimally efficacious dose in a mouse CFA inflammatory joint pain model. Based on population PK simulations, a 100 mg IV Q4W dosing regimen is predicted to yield a  $C_{trough}$  increasing from ~8 mg/L at the end of the first dosing interval to ~11 mg/L at the end of the last dosing interval, with a cumulative AUC ~93-fold less than that observed for the 13-week monkey NOAEL.

### 3.3. Risk-Benefit

Based on the FIH study, the doses selected for this study (Section 3.2.2), and the extensive medical monitoring that will be performed (Section 8.2.3), the sponsor expects minimal risk to the study participants. Patients with a diagnosis of OA of the knee who participate in this study may benefit from study drug administration by experiencing relief of pain due to OA. Considering the unmet medical need for patients with pain due to OA, the sponsor considers the benefit-risk to be positive for this study.

Additional risk-benefit assessment information on REGN5069 may be found in the current version of the Investigator's Brochure.

## 4. STUDY ENDPOINTS AND VARIABLES

### 4.1. Primary and Secondary Endpoints

#### 4.1.1. Primary Endpoint

The primary endpoint of the study is the change from baseline to week 12 in the WOMAC pain subscale score in patients treated with REGN5069 compared to patients treated with placebo.

#### 4.1.2. Secondary Endpoints

##### 4.1.2.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study are:

- Change from baseline to week 12 in the WOMAC total score (based on the full survey) in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in the WOMAC physical function subscale score in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in the Patient Global Assessment score in patients treated with REGN5069 compared to patients treated with placebo
- Change from baseline to week 12 in WOMAC stiffness subscale score in patients treated with REGN5069 compared to patients treated with placebo
- Percentage of patients treated with REGN5069, compared to that of patients treated with placebo, who had a response at week 12, with response defined as an improvement by  $\geq 30\%$  in the WOMAC pain subscale scores

##### 4.1.2.2. Secondary Safety Endpoints

The secondary safety endpoints of the study are:

- The incidence of treatment-emergent adverse events (TEAEs) in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration

- The incidence of imaging abnormalities consistent with accelerated arthropathies as assessed by X-ray and MRI in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration
- Presence of anti-REGN5069 antibody development in patients treated with REGN5069 compared to patients treated with placebo throughout the study duration

#### 4.1.3. Exploratory Endpoints

The exploratory endpoints of the study are:

- Area under the curve for WOMAC pain subscale score (for the 12-week treatment period) for patients treated with REGN5069 compared to patients treated with placebo
- Change in high sensitivity C-reactive protein (hsCRP) from baseline to week 12 in patients treated with REGN5069 compared to patients treated with placebo
- Change in alkaline phosphatase from baseline to week 12 in patients treated with REGN5069 compared to patients treated with placebo
- Conditional endpoints: if a mean 10% increase in alkaline phosphatase is observed at week 4, CTX-1, P1NP, Osteocalcin, C1M, and C3M will be measured and change from baseline to week 12 in patients treated with REGN5069 compared to patients treated with placebo will be exploratory endpoints
- Change in gait and functional mobility parameters recorded by a wearable insole device from baseline to week 12 in a subset of patients treated with REGN5069 compared to patients treated with placebo at participating sites

#### 4.2. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc.), disease characteristics including medical and surgical history, and medication history for each patient.

#### 4.3. Pharmacokinetic Variables

The PK variable is the concentration of functional REGN5069 in serum at each time point that sample is collected ([Table 1](#)).

#### 4.4. Immunogenicity Variables

The immunogenicity variables are ADA status and titer for analyzed samples collected at the specified study site visits ([Table 1](#)).

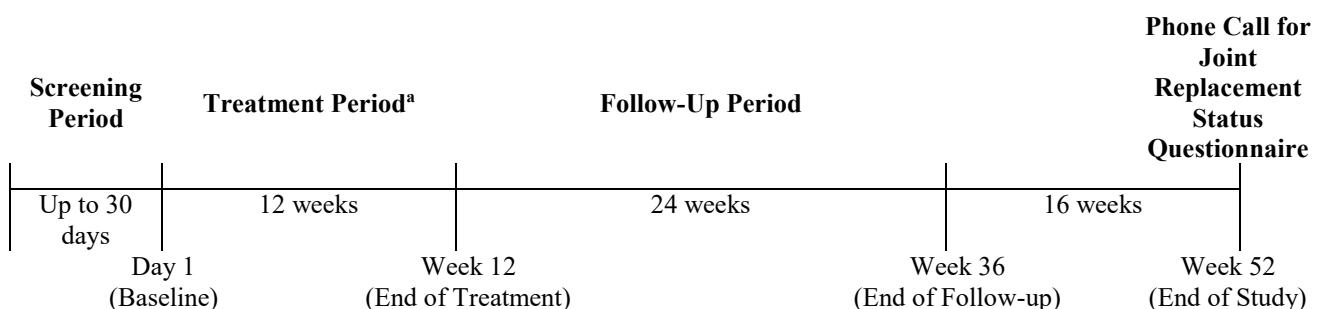
## 5. STUDY DESIGN

### 5.1. Study Description and Duration

This multicenter phase 2 study is planned for US and ex-US study site locations. The study consists of a screening period of up to 30 days, followed by a 12-week randomized, double-blind, placebo-controlled treatment period, a 24-week follow-up period, and an end-of-study phone call approximately 52 weeks after the first dose of study drug (Figure 1). The purpose of the end-of-study phone call is to determine whether a patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer. Thus, each patient will be enrolled in the study for approximately 56 weeks, including the screening period and the period up to the end-of-study phone call. Patients will be randomized in a 1:1:1 ratio to receive a low dose of REGN5069 at 100 mg IV Q4W, a high dose of REGN5069 at 1000 mg IV Q4W, or matching placebo Q4W (Section 7). The index knee joint is defined as the knee joint affected by OA and selected for primary assessment for this study. Randomization will be stratified by Kellgren-Lawrence (K-L) category (2-3 vs 4) of the index knee joint at the screening visit and participation in the Moticon sub-study (yes vs no). The use of the stratification factor based on participation in the Moticon sub-study ensures balance in the treatment assignments within the Moticon sub-study.

Efficacy will be measured according to the assessments detailed in Section 8.2.2. Safety will be assessed according to the procedures in Section 8.2.3.

**Figure 1: Study Flow Diagram**



a - Study drug will be administered every 4 weeks throughout the 12-week treatment period. Thus, study drug will be administered at the day 1 (baseline) visit and at the week 4 and week 8 visits.

#### 5.1.1. Study Stopping Rules

An independent Data Monitoring Committee (IDMC) will monitor unblinded data (Section 5.3.1). Based on these reviews in the context of the totality of evidence, if there are significant concerns at any time regarding a safety issue, the IDMC may make a recommendation to the sponsor to temporarily pause, alter, or terminate the study. Once recommendations from the IDMC have been received, further discussions may be conducted, if appropriate, and the sponsor will determine if these or other actions should be taken.

### **5.1.2. End of Study Definition**

The end of study is defined as the date when the last patient completes the last phone call, withdraws from the study, or is lost to follow-up (ie, the patient can no longer be contacted by the investigator).

### **5.2. Planned Interim Analysis**

No interim analysis is planned. Upon completion of 12 weeks of treatment for all patients, a 12-week analysis will be performed for the primary efficacy endpoint.

### **5.3. Study Committees**

#### **5.3.1. Independent Data Monitoring Committee**

An IDMC will be implemented in the study. The IDMC will meet periodically to review unblinded data as the study progresses, and based upon the findings, will make recommendations to the sponsor about the conduct of the study. The IDMC will be comprised of independent statistical and medical/medical imaging experts. Further details will be defined in the IDMC charter.

## **6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS**

### **6.1. Number of Patients Planned**

Up to approximately 240 patients are planned for enrollment in this study.

### **6.2. Study Population**

Men and women who are at least 40 years of age at the time of study entry with a clinical diagnosis of OA of the knee based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score  $\geq 2$ ) at the index knee joint.

#### **6.2.1. Inclusion Criteria**

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female,  $\geq 40$  years of age at the screening visit
2. Generally in good health at the screening visit
3. Body mass index (BMI)  $\leq 39 \text{ kg/m}^2$  at the screening visit
4. Clinical diagnosis of OA of the knee based on the American College of Rheumatology criteria ([Altman, 1986](#)) with radiologic evidence of OA (K-L score  $\geq 2$ ) at the index joint at the screening visit
  - The index joint is defined as the joint with OA under evaluation for this study
  - A joint that has previously undergone joint replacement surgery cannot be the index joint

- A joint previously surgically modified within the past year cannot be the index joint
- If a patient has a K-L score of  $\geq 2$  at more than 1 knee joint, the index joint is the joint with the greatest WOMAC pain subscore at the screening visit. If both knee joints have a K-L score of  $\geq 2$  and the same WOMAC pain subscore, the index joint is the joint with the greater K-L score. If both knee joints have a K-L score of  $\geq 2$ , the same WOMAC pain subscores, and the same K-L scores, then the investigator may choose 1 of these joints as the index joint.

5. Moderate-to-severe pain in the index joint defined as a WOMAC pain subscore of  $\geq 4$  at both the screening and baseline visits
6. A history of inadequate pain relief from or intolerance to analgesics used for OA as defined by:
  - inadequate pain relief from acetaminophen, and
  - intolerance to or inadequate pain relief from at least 1 oral NSAID, and
  - intolerance to or inadequate pain relief from at least 1 opioid, or unwillingness to take opioid therapy or lack of access to opioid therapy
7. History of regular use of analgesic medications for OA pain (defined as use with regular frequency with an optimal regimen over a period of at least 4 weeks), including NSAIDs, selective cyclooxygenase 2 inhibitors, opioids, acetaminophen, or combinations thereof within 2 years prior to screening
8. No use of opioid medications for at least 4 weeks prior to the screening visit
9. Willing to discontinue current acetaminophen or NSAID medications (oral or topical; except up to 150 mg/day of aspirin, which is permitted for cardiac prophylaxis) starting at the screening visit through the end of the study treatment
10. Willing to maintain current activity and exercise levels throughout the study
11. Willing to provide follow-up information related to any joint replacement surgery that occurs within the period of time covered by the patient's intended participation in the study
12. Willing to consent to providing joint material and having histological and molecular analyses conducted on this material if the patient undergoes a joint replacement surgery while participating in the study
13. Willing and able to comply with clinic visits and study-related procedures
14. Provide informed consent signed by study patient or legally acceptable representative
15. Able to understand and complete study-related questionnaires

#### 6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Diagnosis of systemic diseases that may affect joints, including but not limited to inflammatory joint diseases, pseudogout, endocrinopathies (with exception of

hypothyroidism), lupus erythematosus, rheumatoid arthritis, joint infections, neuropathic disorders, avascular necrosis, Paget's disease, renal osteodystrophy, sickle cell disease, including S-C disease and S-β thalassemia, or tumors.

Note: Patients with a history of hypothyroidism must have thyroid-stimulating hormone levels measured and must be in an euthyroid state to be eligible for study participation.

2. History or presence of osteonecrosis, destructive arthropathy, neuropathic joint arthropathy, pathologic fractures in any shoulder, hip, or knee joint(s), hip dislocation (prosthetic hip dislocation is eligible), or knee dislocation (patella dislocation is eligible) at the screening visit. Presence of subchondral insufficiency fracture on screening films or MRI as assessed by the central imaging reader.
3. Trauma to the index joint within 30 days prior to the screening visit, significant enough in the opinion of the investigator to interfere with response to investigational agent
4. Active fibromyalgia, as diagnosed by the investigator and/or documented in the patient's medical history, regional pain caused by lumbar or cervical compression with radiculopathy or other moderate-to-severe pain that may confound assessments or self-evaluation of the pain associated with OA
5. Is scheduled for a joint replacement surgery to be performed during the study period
6. Not suitable for MRI scan in the judgement of the investigator
7. Received an intra-articular injection of hyaluronic acid in any joint within 90 days prior to the screening visit
8. Systemic (ie, IV, oral, or intramuscular) corticosteroids within 30 days prior to the screening visit. Intra-articular corticosteroids in the index joint within 12 weeks prior to the screening visit, or to any other joint within 30 days prior to the screening visit (topical, intranasal, or inhaled corticosteroids are permitted).
9. Use of a monoamine reuptake or a monoamine oxidase inhibitor (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors) for treatment of pain within 4 weeks prior to the screening visit.

Notes:

- Use of a monoamine reuptake or monoamine oxidase inhibitor is acceptable if used for treatment of anxiety and/or depression at a stable dose during at least 3 months prior to screening
- If in the judgement of an investigator a monoamine reuptake or a monoamine oxidase inhibitor is used for treatment of both pain and anxiety/depression at a stable dose during at least 3 months prior to screening, use of the monoamine reuptake or monoamine oxidase inhibitor is acceptable if the investigator is able to provide appropriate documentation (eg, medical records with appropriate diagnoses, clinical opinions of the patient's treating physicians, documentation of the investigator's clinical opinion).

10. History or presence at the screening visit of multiple sclerosis, autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy

11. Significant concomitant illness including, but not limited to, psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in the study
12. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening
13. Resting heart rate of <45 beats per minute (bpm) (by vital sign assessment or as captured during electrocardiogram [ECG] assessment) or history or presence of second- or third-degree heart block at the screening visit. Resting heart rate may be rechecked up to 2 times at the screening visit.
14. History or presence of orthostatic hypotension at the screening visit. If the initial assessment for orthostatic hypotension is positive, orthostatic vital signs can be repeated up to 2 more times to confirm orthostatic hypotension prior to making the decision to exclude the patient. Refer to Section 8.2.3.2 for more information regarding this assessment.
15. History of poorly controlled hypertension, as defined by:
  - Systolic blood pressure  $\geq 180$  mm Hg or diastolic blood pressure  $\geq 110$  mm Hg at the screening visit
  - Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack, peripheral arterial disease, and moderate-to-advanced retinopathy [hemorrhages or exudates, papilledema]).

Note: Blood pressure can be rechecked twice at the screening visit.

16. History of myocardial infarction, acute coronary syndromes, transient ischemic attack, or cerebrovascular accident within 12 months prior to the screening visit
17. Poorly controlled diabetes (defined as hemoglobin A1c [HbA1c]  $>9.0\%$ ) at the screening visit. This parameter may be re-checked once during the screening period.
18. Known history of human immunodeficiency virus (HIV) infection, except for patients who are stable on treatment for at least 1 year prior to the screening visit
19. Known history of infection with hepatitis B virus. Patients with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen.
20. Known history of infection with hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test.
21. History or presence of malignancy within approximately 5 years prior to screening or continuing active treatment of malignancy regardless of history, except patients who have been treated successfully with no recurrence for  $>1$  year of basal or squamous cell carcinoma of the skin or in situ cervical cancer
22. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies

23. History of (within approximately 5 years prior to the screening visit) or current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication, as documented in the medical history or in the judgement of the investigator
24. History of cannabis use for the treatment of pain or for recreational use within approximately the past 6 months prior to the screening visit
25. Participation in any clinical research study evaluating another investigational drug within 30 days or at least 5 half-lives, whichever is longer, of the investigational drug, prior to the screening visit
26. History of exposure to an anti-NGF treatment
27. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor
28. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug treatment period and for at least 9 months after the last dose of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for at least 9 months after the last dose of study drug.
29. Women of childbearing potential (WOCBP)\* who have a positive pregnancy test result, or who do not have their pregnancy test results at baseline.
30. Pregnant or breastfeeding women.
31. Women of childbearing potential\* who are unwilling to practice highly effective contraception from the screening visit until at least 9 months after the last dose of study drug. Highly effective contraceptive measures include:
  - a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
  - b. intrauterine device; intrauterine hormone-releasing system
  - c. bilateral tubal ligation
  - d. vasectomized partner
  - e. and/or sexual abstinence<sup>†,‡</sup>

\* Postmenopausal women must be amenorrheic for at least 12 months and must have follicle-stimulating hormone (FSH) in the postmenopausal range in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not

acceptable methods of contraception. Female condom and male condom should not be used together.

32. Use of genicular nerve block or any similar procedure(s) within 3 months of the screening visit

### **6.3. Premature Withdrawal from the Study**

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section [8.1.3](#).

Rules for discontinuation of study treatment are discussed in Section [7.3.2](#).

### **6.4. Replacement of Patients**

Patients prematurely withdrawn from the study or study drug will not be replaced.

## **7. STUDY TREATMENTS**

### **7.1. Investigational Treatments**

REGN5069 will be supplied for this study in blinded kits as follows:

- REGN5069 lyophilized powder, 265 mg in a vial
- REGN5069 lyophilized powder, placebo in a vial

Instructions for dose preparation and study drug administration are provided in the pharmacy manual.

Randomized patients will receive a total of 3 fixed-dose IV infusions of either REGN5069 at 100 mg, REGN5069 at 1000 mg, or placebo (depending on their treatment assignment) Q4W during the 12-week treatment period at the visits indicated in the Schedule of Events ([Table 1](#)).

### **7.2. Rescue Treatment**

Starting at the screening visit until after the week-24 study visit is completed, acetaminophen is the only study-permitted rescue medication. Acetaminophen tablets of selected brand and strength will be provided to patients by the study site for use as rescue medication for breakthrough OA pain. In advance of initiating the study, each study site must consult with the sponsor and select the brand and the strength of acetaminophen tablets that will be dispensed to patients as rescue medication. In the event that pain relief for OA pain is inadequate, patients will take acetaminophen, as needed, in accordance with the instructions provided with the medication

by each study site, with a maximum of 3000 mg/day. To prevent liver damage, the maximum allowed daily dose of 3000 mg of acetaminophen must not be exceeded and excessive alcohol consumption must be avoided. The use of rescue medication is not allowed for 48 hours prior to the start of or during a scheduled study visit to minimize the confounding effects of rescue medication on efficacy measures.

### **7.3. Dose Modification and Study Treatment Discontinuation Rules**

#### **7.3.1. Dose Modification**

Dose modification for an individual patient is not allowed.

#### **7.3.2. Study Drug Discontinuation**

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits and to participate in all study phone calls per the visit schedule.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section [8.1.3](#).

##### **7.3.2.1. Reasons for Permanent Discontinuation of Study Drug**

Study drug dosing will be permanently stopped in the event of:

- Continued noncompliance with the protocol-defined maximum allowed dosage of acetaminophen
- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- If there are specific types of liver dysfunction (eg, Hy's law is met). Hy's law consists of elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) by 3-fold of upper limit of normal (ULN) or more and elevation of serum total bilirubin by 2-fold of ULN or more and there are no other reasons to explain observed elevations in aminotransferases and bilirubin.
- Patient withdraws consent

### **7.4. Management of Acute Reactions**

#### **7.4.1. Acute Intravenous Infusion Reactions**

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section [9.4.1](#)) and graded using the grading scales (as instructed in Section [9.5.1](#)).

##### **7.4.1.1. Interruption of the Intravenous Infusion**

The infusion should be interrupted if any of the following AEs are observed:

- cough

- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate or based on the clinical judgement of the investigator.

If investigators feel there is a medical need for treatment or discontinuation of the infusion, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

#### 7.4.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis\*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

\*Consider anaphylaxis if the following is observed ([Sampson, 2006](#)): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

## 7.5. Method of Treatment Assignment

Up to approximately 240 patients will be randomized in a 1:1:1 ratio (approximately 80 patients per treatment group) to receive REGN5069 at 100 mg IV Q4W, REGN5069 at 1000 mg IV Q4W, or matching placebo Q4W according to a central randomization scheme provided by an Interactive Web Response System (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified by K-L category (2-3 vs 4) of the index knee joint at the screening visit and participation in the Moticon sub-study (yes vs no).

### 7.5.1. Blinding

Study patients, the principal/coordinating investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron study team and contract research organization (CRO) personnel who are in regular contact with the study sites will remain blinded to all patient randomization assignments.

Blinded study drug kits coded with a drug numbering system will be used. To maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody and PK results will not be communicated to the sites before the end of the study and the final database lock, and the sponsor's operational team will not have access to results associated with patient identification until after the final database lock.

Selected individuals not involved in the conduct of the study may have access to unblinded data (individual treatment assignments) as needed for safety review or other data review. No study personnel involved in the day-to-day conduct of the study will have access to any individual unblinded data before the database is locked for this study.

### 7.5.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent upon knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected patients will be unblinded.
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IWRS, which will notify Regeneron.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment

assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

## **7.6. Treatment Logistics and Accountability**

### **7.6.1. Packaging, Labeling, and Storage**

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

### **7.6.2. Supply and Disposition of Treatments**

Study drug will be shipped at a temperature of 2°C to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee for destruction.

### **7.6.3. Treatment Accountability**

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and
- returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

### **7.6.4. Treatment Compliance**

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

## **7.7. Concomitant Medications and Procedures**

Any treatment administered and/or procedures performed from screening to the end of the follow-up period will be considered concomitant medication and/or procedures, respectively. This includes medications and/or procedures that were started before the study and are ongoing during the study.

### 7.7.1. Prohibited Medications and Procedures

Patients will be required to discontinue all non-study-permitted pain medication (oral or topical) starting at the screening visit until after completion of the week-24 study visit. Concomitant medications that contain NSAIDs are prohibited from the screening visit until after completion of the week-24 study visit. This applies even if a patient discontinues study drug prematurely but remains in the study to participate in the remaining study visits. The only exception is aspirin/5-aminosalicylic acid, which is permitted for cardiac prophylaxis (Section 7.7.2). Opioid analgesic medications (including tramadol) are prohibited starting at least 4 weeks prior to the screening visit until the end of the follow-up period with no exceptions.

Other excluded medications/procedures starting at the screening period include:

- Any other investigational agent
- Medical or regular recreational use of marijuana
- Chondroitin sulfate
- Glucosamine
- Hyaluronic Acid Intra-articular injections
- Anticoagulants and antiplatelets (eg, warfarin, heparins, factor Xa inhibitors, thrombin inhibitors, aspirin >150 mg daily, clopidogrel)
- Muscle relaxants including cyclobenzaprine, carisoprodol, orphenadrine, tizanidine (see Section 7.7.2 for permitted muscle relaxants)
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus (topical tacrolimus allowed)
- Azathioprine, sulfasalazine, hydroxychloroquine
- IL-6 or IL-6 receptor antagonists
- Abatacept, ustekinumab
- Tumor necrosis factor antagonists
- IL-1 inhibitors, including diacerein
- PDE-4 and Jak-kinase inhibitors
- Genicular nerve block and any other similar procedures (prohibited from within 3 months of the screening visit and up to the last study site visit in the follow-up period)

### 7.7.2. Permitted Medications and Procedures

Patients receiving any chronic medication therapy must be on a stable dose of such medication for at least 3 months prior to the screening visit except for the prohibited medications listed in Section 7.7.1.

Monoamine reuptake inhibitors (including selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors) and tricyclic antidepressants, are permitted for non-pain-related treatment.

Low-dose aspirin/5-aminosalicylic acid (up to 150 mg/day) for cardiac prophylaxis is also permitted, per local guidelines. Acetaminophen taken acutely for treatment of non-OA pain or fever is also permitted; however, the total daily dosage limits cannot be exceeded, regardless of the reason for acetaminophen use. During the treatment period and through the week-24 study visit, acetaminophen use will be captured in the diary; use for relief of pain other than pain due to OA will be reported in the diary as “other.” During the screening period and after the week-24 study visit is completed, acetaminophen taken for any reason will be reported as concomitant medication.

Topical steroids and topical calcineurin inhibitors are permitted.

Muscle relaxants, such as Skelaxin® (metaxalone) and others, are permitted. Prohibited muscle relaxants are listed in Section [7.7.1](#).

Physical therapies (such as transcutaneous electrical nerve stimulation and acupuncture) are permitted during the study, provided that patients have been on a stable regimen for at least 4 weeks prior to entering the trial and that they expect to maintain this regimen until the end of the follow-up period.

Use of mobility aids (such as canes, crutches, and joint stabilization appliances) are also permitted, provided that patients have been on a stable level of usage for at least 4 weeks prior to screening. Patients will be encouraged to maintain their use of such aids at a stable level starting from the screening visit until the week-24 visit is completed. Use of mobility aids should be recorded in the CRF.

## **8. STUDY SCHEDULE OF EVENTS AND PROCEDURES**

### **8.1. Schedule of Events**

Study assessments and procedures are presented by study period and visit in [Table 1](#).

Table 1: Schedule of Events

|   | Screening Period  | Treatment Period  |           |            |            |            |             |                            | Follow-up Period |             |             |             |             |              |                            | EOS         |
|---|-------------------|-------------------|-----------|------------|------------|------------|-------------|----------------------------|------------------|-------------|-------------|-------------|-------------|--------------|----------------------------|-------------|
|   |                   | Base-line Visit 2 | Visit 3   | Visit 4    | Visit 5    | Visit 6    | EOT Visit 7 | ET/JR Pre-op <sup>10</sup> | Visit 8          | PC 1        | Visit 9     | PC 2        | PC 3        | EOF Visit 10 | ET/JR Pre-op <sup>10</sup> |             |
| Study Procedure/Visit   | Screening Visit 1 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Study Week  |                   |                   | Wk 1      | Wk 2       | Wk 4       | Wk 8       | Wk 12       |                            | Wk 16            | Wk 20       | Wk 24       | Wk 28       | Wk 32       | Wk 36        |                            | Wk 52       |
| Study Day (Visit Window, days)                                  | Up to 30 days     | 1                 | 8<br>(±1) | 15<br>(±3) | 29<br>(±7) | 57<br>(±7) | 85<br>(±7)  |                            | 113<br>(±7)      | 141<br>(±7) | 169<br>(±7) | 197<br>(±7) | 225<br>(±7) | 253<br>(±7)  |                            | 365<br>(±7) |
| <b>Screening/Baseline</b>                                       |                   |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Inclusion/Exclusion   | X                 | X                 |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Informed consent  | X                 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Medical and medication history                                  | X                 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Demographics  | X                 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Height  | X                 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Weight  | X                 |                   |           |            |            |            |             | X                          | X                |             |             |             |             | X            | X                          |             |
| Dispense patient diary and train <sup>1</sup>                   | X                 | X                 |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Randomization   |                   | X                 |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| <b>Efficacy Assessments<sup>2</sup></b>                         |                   |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| WOMAC Pain Subscale   | X                 |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| WOMAC Full Survey   |                   | X                 | X         | X          | X          | X          | X           | X                          | X                |             | X           |             |             | X            | X                          |             |
| Patient Global Assessment of OA                                 |                   | X                 | X         | X          | X          | X          | X           | X                          | X                |             | X           |             |             | X            | X                          |             |
| <b>Treatment Procedures</b>                                     |                   |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Check diary for recording of rescue medication use <sup>3</sup> |                   |                   | X         | X          | X          | X          | X           | X                          | X                |             | X           |             |             |              | X                          |             |
| Concomitant therapies   | X                 | X                 | X         | X          | X          | X          | X           | X                          | X                | X           | X           | X           | X           | X            | X                          |             |
| IV study drug administration <sup>4</sup>                       |                   | X                 |           |            | X          | X          |             |                            |                  |             |             |             |             |              |                            |             |
| <b>Safety Assessments</b>                                       |                   |                   |           |            |            |            |             |                            |                  |             |             |             |             |              |                            |             |
| Vital signs <sup>5</sup>  | X                 | X                 | X         | X          | X          | X          | X           | X                          | X                |             | X           |             |             |              |                            |             |
| Orthostatic vital   | X                 | X                 | X         | X          | X          | X          | X           | X                          | X                |             | X           |             |             | X            | X                          |             |

|  | Screening Period            | Treatment Period  |           |         |           |           |                     |                             | Follow-up Period |          |           |          |          |                |                             | EOS      |
|--|-----------------------------|-------------------|-----------|---------|-----------|-----------|---------------------|-----------------------------|------------------|----------|-----------|----------|----------|----------------|-----------------------------|----------|
|  |                             | Base-line Visit 2 | Visit 3   | Visit 4 | Visit 5   | Visit 6   | EOT Visit 7         | ET/JR Pre-op <sup>10</sup>  | Visit 8          | PC 1     | Visit 9   | PC 2     | PC 3     | EOF Visit 10   | ET/JR Pre-op <sup>10</sup>  |          |
| Study Procedure/Visit  | Screening Visit 1           |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| Study Week   |                             |                   | Wk 1      | Wk 2    | Wk 4      | Wk 8      | Wk 12               |                             | Wk 16            | Wk 20    | Wk 24     | Wk 28    | Wk 32    | Wk 36          |                             | Wk 52    |
| Study Day (Visit Window, days)   | Up to 30 days               | 1                 | 8 (±1)    | 15 (±3) | 29 (±7)   | 57 (±7)   | 85 (±7)             |                             | 113 (±7)         | 141 (±7) | 169 (±7)  | 197 (±7) | 225 (±7) | 253 (±7)       |                             | 365 (±7) |
| sign assessment <sup>5</sup>   |                             |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| Physical examination with joint exam   | X (full)                    | X (full)          | X (brief) |         | X (brief) | X (brief) | X (full)            | X (full)                    | X (brief)        |          | X (brief) |          |          | X (full)       | X (full)                    |          |
| Electrocardiogram  | X                           |                   | X         |         |           |           | X                   | X                           |                  |          |           |          |          |                |                             |          |
| Neurologic examination   | X (full)                    | X (brief)         | X (brief) |         |           |           | X (full)            | X (full)                    | X (brief)        |          | X (brief) |          |          | X (full)       | X (full)                    |          |
| Radiograph collection (bilateral knees, hips, and shoulders, unless otherwise stated) <sup>6</sup> | X                           |                   |           |         |           |           | X (index knee only) | X <sup>7</sup>              |                  |          |           |          |          | X              | X <sup>7</sup>              |          |
| MRI <sup>8</sup>   | X (index knee) <sup>9</sup> |                   |           |         |           |           | X (index knee)      | X (index knee) <sup>7</sup> |                  |          |           |          |          | X (index knee) | X (index knee) <sup>7</sup> |          |
| Joint pain questionnaire <sup>2</sup>  |                             |                   |           | X       | X         | X         | X                   | X                           | X                | X        | X         | X        | X        | X              | X                           |          |
| Knee Society Score (for JR follow-up) <sup>2,10</sup>  |                             |                   |           |         |           |           |                     | X                           |                  |          |           |          |          |                |                             | X        |
| Adverse events   | →                           |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| JR status questionnaire  |                             |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             | X        |
| <b>Laboratory Testing</b>  |                             |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| Drug and alcohol test <sup>11</sup>  | X                           | X                 |           |         | X         | X         | X                   | X                           |                  |          | X         |          |          | X              | X                           |          |
| Hematology <sup>12</sup>   | X                           | X                 |           |         | X         | X         | X                   | X                           | X                |          | X         |          |          | X              | X                           |          |
| Blood chemistry <sup>12</sup>  | X                           | X                 |           |         | X         | X         | X                   | X                           | X                |          | X         |          |          | X              | X                           |          |
| ESR  | X                           |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| HbA1c <sup>12</sup>  | X                           |                   |           |         |           |           |                     |                             |                  |          |           |          |          |                |                             |          |
| Urinalysis   | X                           | X                 |           |         | X         | X         | X                   | X                           | X                |          | X         |          |          |                |                             |          |
| Pregnancy test (for  | X                           | X                 | X         | X       | X         | X         | X                   | X                           | X                |          | X         |          |          | X              | X                           |          |

|   | Screening Period  | Treatment Period  |         |         |                 |                 |             |                            | Follow-up Period |          |          |          |          |              |                            | EOS      |
|---|-------------------|-------------------|---------|---------|-----------------|-----------------|-------------|----------------------------|------------------|----------|----------|----------|----------|--------------|----------------------------|----------|
|   |                   | Base-line Visit 2 | Visit 3 | Visit 4 | Visit 5         | Visit 6         | EOT Visit 7 | ET/JR Pre-op <sup>10</sup> | Visit 8          | PC 1     | Visit 9  | PC 2     | PC 3     | EOF Visit 10 | ET/JR Pre-op <sup>10</sup> |          |
| Study Procedure/Visit                       | Screening Visit 1 |                   |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| Study Week                                  |                   |                   | Wk 1    | Wk 2    | Wk 4            | Wk 8            | Wk 12       |                            | Wk 16            | Wk 20    | Wk 24    | Wk 28    | Wk 32    | Wk 36        |                            | Wk 52    |
| Study Day (Visit Window, days)              | Up to 30 days     | 1                 | 8 (±1)  | 15 (±3) | 29 (±7)         | 57 (±7)         | 85 (±7)     |                            | 113 (±7)         | 141 (±7) | 169 (±7) | 197 (±7) | 225 (±7) | 253 (±7)     |                            | 365 (±7) |
| WOCBP <sup>13</sup>                         | (serum)           | (urine)           | (urine) | (urine) | (urine)         | (urine)         | (urine)     | (serum)                    | (urine)          | (urine)  | (urine)  | (urine)  | (serum)  | (serum)      | (serum)                    |          |
| FSH <sup>14</sup>                           | X                 |                   |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| <b>PK, Biomarker, and Research Samples</b>  |                   |                   |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| PK sample                                   |                   | X <sup>15</sup>   | X       | X       | X <sup>15</sup> | X <sup>15</sup> | X           | X                          | X                |          | X        |          |          | X            | X                          |          |
| ADA samples                                 |                   | X (pre-dose)      |         |         |                 |                 | X           | X                          |                  |          |          |          |          | X            | X                          |          |
| hsCRP <sup>12</sup>                         |                   | X                 | X       | X       | X               | X               | X           | X                          |                  |          | X        |          |          | X            | X                          |          |
| Research serum/plasma samples <sup>12</sup> |                   | X                 | X       | X       | X               | X               | X           | X                          |                  |          | X        |          |          | X            | X                          |          |
| DNA <sup>16</sup>                           |                   | X                 |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| RNA (whole blood)                           |                   | X                 |         | X       |                 |                 |             | X                          | X                |          |          |          |          |              |                            |          |
| <b>Moticon Insole Sub-study</b>             |                   |                   |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| Moticon sub-study informed consent          | X                 |                   |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| Moticon insole training <sup>17</sup>       |                   | X                 |         |         |                 |                 |             |                            |                  |          |          |          |          |              |                            |          |
| Moticon insole recording <sup>18</sup>      |                   | X                 |         |         |                 |                 |             | X                          | X                |          |          |          |          |              |                            |          |

ADA: Anti-drug antibody

HbA1c: Hemoglobin A1c (Glycated hemoglobin)

Pre-op: Pre-operative

EOF: End of follow-up

hsCRP: high sensitivity C-reactive protein

V: Visit

EOS: End of study

IV: Intravenous

Wk: Week

EOT: End of treatment

JR: Joint replacement

WOCBP: Women of childbearing potential

ESR: Erythrocyte sedimentation rate

MRI: Magnetic resonance imaging

WOMAC: Western Ontario and McMaster Osteoarthritis Index

ET: Early termination

PC: Phone call

FSH: Follicle-stimulating hormone

PK: Pharmacokinetic

**8.1.1. Footnotes for the Schedule of Events Table 1**

1. The patient will receive a diary in which he/she will record use of study-permitted rescue medication from baseline through the week-24 study visit. The patient will receive training on use of the diary (can be conducted at the baseline visit or earlier at the discretion of the investigator). The patient will be required to bring the diary to each study visit and it will be collected at the week-24 visit, or early if the patient terminates the study early.
2. Questionnaires (including WOMAC, Patient Global Assessment score, joint pain questionnaire, and Knee Society Score, if necessary) will be completed by the patient. These assessments should be the first procedures performed during study site visits at the indicated visits.
3. At each study visit indicated in the schedule of events table (Table 1), study site personnel will check that the patient is recording his/her use of acetaminophen as the study-permitted rescue medication in the patient diary. Retraining on patient diary usage may be requested at any visit during the study, as needed. The diary will be returned at the week-24 visit or at the early termination visit, if applicable.
4. Study drug administration will be the last procedure at each dosing visit, and will be done after all laboratory samples have been collected (except for those specifically stated for collection after study drug administration), and after all study assessments and procedures are performed. Patients will be observed in the clinic for 1 hour after study drug administration.
5. Refer to Section 8.2.3.1 for more instructions surrounding the vital sign assessment and to Section 8.2.3.2 for instructions for rechecking orthostatic vital sign assessments and for defining orthostatic hypotension.
6. In addition to scheduled imaging, radiographs should be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator is inconsistent with the normal progression of OA or lasts at least 2 weeks (or less at the discretion of the investigator). Based on the imaging results, a patient may be discontinued from study drug. If this occurs, the patient should be asked to remain in the study and participate in study visits per the visit schedule.
7. Early Termination: Imaging assessments (X-rays of bilateral knees, hips, and shoulders and MRI of the index knee) need to be repeated only if it has been >30 days since the joints were last imaged. If it has been ≤30 days since the joints were last imaged, imaging assessment may be completed at the discretion of the investigator.
8. In addition to scheduled MRIs, an MRI should be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator is inconsistent with the normal progression of OA, lasts at least 2 weeks (or less at the discretion of the investigator), and if the X-rays are inconclusive.
9. After the patient has otherwise met study eligibility criteria assessed during the screening period, an MRI of the index knee will be performed prior to the baseline visit. Confirmation that the images have been accepted and confirmed query-free by the central reader must be received by the site before the baseline visit. Confirmation that there are

no exclusionary findings on the MRI must be received from the central reader before a patient can be randomized.

10. In the event that a patient must undergo joint replacement surgery during the study up to the end of the follow-up period at week 36, the patient will complete the early termination/joint replacement pre-operative visit as per [Table 1](#) Schedule of Events and the procedures outlined in the schedule of events for joint replacement surgery follow-up ([Table 2](#)). The early termination/joint replacement pre-operative visit should be completed before the joint replacement surgery, if possible.
11. In the event of a confirmed positive drug screen result for opiates and/or alcohol at screening, the patient will be excluded. A confirmed positive drug screen result for opiates and/or alcohol prior to the initial dose of study drug and/or during the treatment period must be discussed with the sponsor prior to administration of the next dose of study drug once the results are available.
12. Blood samples to be obtained after at least approximately an 8-hour fast.
13. In the event of a positive urine pregnancy test result, a serum pregnancy test should be performed. If the serum pregnancy test is negative, the patient may continue to receive study drug per the visit schedule. If the serum pregnancy test is positive, the patient should discontinue study drug, but should be asked to return to the clinic for all remaining study visits per the visit schedule.
14. The FSH sample should be collected to confirm the postmenopausal status of a female patient.
15. Two pharmacokinetic samples will be collected: the first sample prior to the dose administration and the second sample within 30 minutes after the end of infusion.
16. Samples for DNA extraction should be collected at the baseline visit (pre-dose), but may be collected at any later study visit.
17. Moticon insole training session will be conducted for patients in the Moticon insole device sub-study only, and will be held at participating clinical sites prior to recording sessions.
18. Moticon insole recording sessions will be conducted for patients in the Moticon insole device sub-study only and will include a 3-minute walking test.

**Table 2: Schedule of Events for Follow-up Period of Patients Who Undergo Joint Replacement Surgery**

|  | <b>Post-Operative<sup>1</sup></b>                                   | <b>Long-Term<sup>1</sup></b>   |
|--|---|--|
|  | <b>Follow-up Visit 1</b><br>4 weeks after joint replacement surgery | <b>Follow-up Visit 2</b><br>20 weeks after joint replacement surgery |
| <b>Follow-up Study Day (Visit window, days)</b>                                  | <b>Follow-up Day 29 (±7)</b>  | <b>Follow-up Day 140 (±7)</b>  |
| Collection of surgically resected tissue for histological and molecular analyses |   | X  |
| <b>Treatment</b>   |   |  |
| Concomitant medications and therapy  | X   | X  |
| <b>Safety</b>  |   |  |
| Medical history related to the joint replacement                                 | X   | X  |
| Adverse events   | →   |  |
| Vital signs  | X   | X  |
| Physical examination with joint exam   | X   | X  |
| Knee Society Score <sup>2</sup>  | X   | X  |
| Radiograph of knees, hips, and shoulders (bilateral)                             |   | X  |

### 8.1.2. Footnotes for Schedule of Events for Follow-up Period of Patients Who Undergo Joint Replacement Surgery (Table 2)

1. Any patient who has joint replacement surgery during the study up to the end of the follow-up period at week 36 will be asked to return to the site at 4 and 20 weeks after the surgery date for safety evaluations. Relevant information related to the surgery will be collected at the week-4 visit, including placement of the prosthesis and healing of the surgical wound. The visit at 20 weeks after surgery will include an assessment of OA progression (including repeat radiographs of both knees) and the collection of any information about joint-related pain or AEs (including joint replacement) that may have taken place since the last clinic visit.
2. Formal post-operative assessment of joint replacements will be done by completing the Knee Society Score questionnaire for knee replacements.

### 8.1.3. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 12) will be asked to return to the clinic for 2 visits: once for an early termination visit consisting of the early termination assessments described in [Table 1](#) and again at the primary endpoint visit (week 12), for studies with a primary efficacy endpoint. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments, only.

### 8.1.4. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

## 8.2. Study Procedures

### 8.2.1. Procedures Performed at the Screening/Baseline Visit

Inclusion and exclusion criteria will be assessed at the screening visit to determine study eligibility, including an assessment of medical and medication history. This will include the determination of whether a patient has a diagnosis of knee OA (Section 8.2.1.1). Height and weight measurements will be recorded at the screening visit to calculate BMI (see Section 8.2.1.2 and Section 8.2.1.3 for details on height and weight measurements, respectively). Demographics will be recorded at the screening visit to characterize the baseline population. Eligible patients are required to sign the informed consent form (ICF) prior to undergoing any study procedures. The inclusion and exclusion criteria will again be assessed at the baseline visit to confirm study eligibility.

Patient diaries will be distributed to eligible and enrolled patients at the baseline visit or prior to the baseline visit if patient's eligibility for the study has been established. Patients will be trained on use of the diary to record daily usage of study-permitted rescue medication in the event of breakthrough OA pain. Patients will be instructed to bring the diary to each study visit.

Randomization will occur for eligible and enrolled patients at the baseline visit (day 1).

#### 8.2.1.1. Determination of Osteoarthritis of the Knee

Diagnosis of OA of the knee will be based on the American College of Rheumatology criteria with radiologic evidence of OA (K-L score  $\geq 2$ ). The American College of Rheumatology clinical and radiographic criteria for the diagnosis of OA of the knee (Altman, 1986) criteria consist of the following combinations:

- Knee pain
- Osteophytes on radiograph
- At least 1 of the following 3 features:
  - Age  $>50$  years
  - Stiffness  $<30$  minutes
  - Crepitus

Erythrocyte sedimentation rate (ESR) will be measured for use as part of the diagnosis for OA, as applicable.

#### 8.2.1.2. Height

Patients should not be wearing shoes during height assessment. Height will be recorded to the nearest 1 cm.

#### 8.2.1.3. Weight

Body weight will be measured at the screening visit for the BMI calculation and throughout the study as a safety procedure at the specified visits (Table 1). Body weight should be measured using calibrated scales and will be recorded to the nearest 0.1 kg. Patients should void (empty

bladder) prior to weight assessment and should only be wearing undergarments and should not be wearing shoes during weight assessments.

## 8.2.2. Efficacy Procedures

### 8.2.2.1. Western Ontario and McMaster Osteoarthritis Index

The WOMAC index is used to assess patients with OA of the knee using 24 parameters and is reported using a Numerical Rating Scale score. This index can be used to monitor the course of a disease or to determine efficacy of study drugs. Patients will complete the WOMAC full survey or the pain subscale (a portion of the full survey) at the time points indicated in [Table 1](#).

### 8.2.2.2. Patient Global Assessment of Osteoarthritis

The Patient Global Assessment of OA is a patient-rated assessment of current disease state on a 5-point Likert scale (1 = very good; 2 = good; 3 = fair; 4 = poor; and 5 = very poor). Patients will complete the assessment scale at the time points indicated in [Table 1](#).

## 8.2.3. Safety Procedures

### 8.2.3.1. Vital Signs

Vital signs include blood pressure, pulse, body temperature, and respiratory rate. Vital signs will be obtained in accordance with the study site procedures at the specified visits ([Table 1](#)). The patient should be resting semi-recumbent for approximately 10 minutes prior to having vital signs obtained. Semi-recumbent vital signs include blood pressure and pulse. If at any visit after the baseline visit the pulse is less than 45 bpm confirmed in up to 2 measurements, an ECG with rhythm strip will be obtained to confirm the heart rate and rhythm.

### 8.2.3.2. Orthostatic Vital Sign Assessment

Orthostatic blood pressure and heart rate are measured with the patient lying semi-recumbent for 10 minutes and after standing for 2 minutes. Prior to starting an assessment of orthostatic blood pressure and heart rate, patients should ambulate for at least 5 minutes. This assessment will be performed at the specified visits ([Table 1](#)).

In case any of the following criteria are met, up to 2 re-checks (within approximately 5 minutes of the original measurement) should be performed (patient should remain standing):

If the semi-recumbent systolic blood pressure is <160 mm Hg, a decrease in the 2-minute standing systolic blood pressure of  $\geq 20$  mm Hg or a decrease in the standing diastolic blood pressure of  $\geq 10$  mm Hg from the semi-recumbent systolic or diastolic blood pressure, respectively

OR

If the semi-recumbent systolic blood pressure is  $\geq 160$  mm Hg, a decrease in the 2-minute standing systolic blood pressure of  $\geq 30$  mm Hg or a decrease in the standing diastolic blood pressure of  $\geq 15$  mm Hg from the semi-recumbent systolic or diastolic blood pressure, respectively

OR

An increase in the 2-minute standing heart rate of  $\geq 30$  bpm from the semi-recumbent heart rate.

An AE of orthostatic vital sign change should be reported if the change is confirmed upon the repeat tests.

If the patient is unable to stand for standing blood pressure measurements due to dizziness or lightheadedness, the patient is considered to have orthostatic hypotension, which should be reported.

#### **8.2.3.3. Physical Examination with Joint Exam**

A full or brief physical examination will be performed according to the site's procedures at the time points in [Table 1](#). Both the full and brief physical examinations will include joint examination. The brief physical examination will include assessment of heart, lungs, abdomen, peripheral pulses, and skin.

#### **8.2.3.4. Electrocardiogram**

A standard 12-lead ECG will be performed at the time points indicated in [Table 1](#), with the patient in the semi-recumbent position for approximately 10 minutes and prior to blood samples being drawn. Heart rate will be recorded from the ventricular rate, and the PR/PQ, QRS, and the QT and QTc intervals will be recorded. The ECG strips/reports will be retained with the source. The following parameters will be recorded in the case report form (CRF): ventricular heart rate, PR/PQ, QRS, QT, and QTc intervals.

#### **8.2.3.5. Neurological Examination**

A full or brief neurological examination will be performed at the time points indicated in [Table 1](#). Neurological findings at baseline that are not exclusionary should be recorded in the medical history. Findings at subsequent visits will be assessed by the investigator to determine if these should be recorded as an AE.

The full neurological examination will cover the following domains: mental status, motor, sensory, cranial nerves, reflexes, and coordination/balance. A brief neurological examination will include assessment of orientation, cranial nerves, sensory and motor function, and basic reflexes. Any clinician at the site qualified to do so may conduct the neurological examination. Whenever possible, the same clinician who conducts the baseline neurological examination should continue to conduct the examinations on a given patient.

#### **8.2.3.6. Imaging**

Radiographs of patients' knees, hips, and shoulders will be taken using a standard approach at the time points indicated in [Table 1](#). In addition to scheduled imaging, radiographs should be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator, is inconsistent with the normal progression of OA and lasts at least 2 weeks (or less at the discretion of the investigator). The investigator is to consult the sponsor prior to scheduling additional imaging.

Magnetic resonance imaging of the index knee will be performed at the time points indicated in [Table 1](#). In addition to scheduled MRIs, an MRI should be considered for worsening joint pain despite treatment with analgesics, which in the opinion of the investigator is inconsistent with the

normal progression of OA and lasts at least 2 weeks (or less at the discretion of the investigator), and if X-rays are inconclusive. The investigator is to consult the sponsor prior to scheduling additional imaging.

If a patient undergoes a joint replacement surgery, patients will have additional radiographs at the time points indicated in [Table 2](#).

Screening and on-study radiographs of the knees and hips will be evaluated for joint space width to identify excessive loss of joint space. In addition, all radiographs and MRI scans will be evaluated for the presence of adjudicated arthropathy.

Detailed procedures will be available in a separate manual provided by the central imaging center. Radiographs or MRIs will be sent to a central reader, where the images will be digitized.

#### **8.2.3.7. Joint Pain Questionnaire**

A joint pain questionnaire will be completed by the patient at the time points indicated in [Table 1](#). For each knee, hip, and shoulder joint, the patient will be prompted to indicate if he or she has experienced pain. A patient report of having experienced pain will serve as a tool to prompt further evaluations as deemed necessary by the investigator.

#### **8.2.3.8. End-of-Study Phone Call for Joint Replacement Status Questionnaire**

An end-of-study phone call will be conducted at approximately 52 weeks after the first dose of study drug ([Table 1](#)). The purpose of the end-of-study phone call is to determine whether a patient underwent, is scheduled for, or is on a waiting list to receive joint replacement surgery, or whether joint replacement was recommended but the patient elected to defer since his/her last in-clinic visit. Patients will also be asked to submit pre-operative imaging (X-ray and MRI, if available) for adjudication and to provide joint material for histological and molecular analyzes, if feasible.

#### **8.2.3.9. Knee Society Score for Joint Replacement Follow-up Only**

The Knee Society Score is an investigator-completed questionnaire that is used to objectively measure a patient's ability to function before ([Table 1](#)) and after ([Table 2](#)) total knee arthroplasty ([Insall, 1989](#)). If possible, the assessment should be completed by the same qualified person throughout the study.

#### **8.2.3.10. Laboratory Testing**

Regeneron or its designee will be responsible for PK, ADA, biomarker, [REDACTED], and pharmacogenetic sample assessments. Other samples may be analyzed by either a central laboratory, local laboratories, or at the study sites.

All samples will be collected before study drug administration (unless otherwise mentioned in the Schedule of Events Table [[Table 1](#)] and associated footnotes [Section [8.1.1](#)]). Missed tests should be reported in the source documents and in the CRF, as appropriate. Central laboratory kits will be provided for sample collection and shipment. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to [Table 1](#). Tests will include:

**Blood Chemistry**

|                |                                  |                              |
|----------------|----------------------------------|------------------------------|
| Sodium         | Total protein, serum             | Total bilirubin              |
| Potassium      | Creatinine                       | Total cholesterol*           |
| Chloride       | Blood urea nitrogen (BUN)        | Triglycerides                |
| Carbon dioxide | Aspartate aminotransferase (AST) | Uric acid                    |
| Calcium        | Alanine aminotransferase (ALT)   | Creatine phosphokinase (CPK) |
| Glucose        | Alkaline phosphatase             |                              |
| Albumin        | Lactate dehydrogenase (LDH)      |                              |

\*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

**Hematology**

|                          |               |
|--------------------------|---------------|
| Hemoglobin               | Differential: |
| Hematocrit               | Neutrophils   |
| Red blood cells (RBCs)   | Lymphocytes   |
| White blood cells (WBCs) | Monocytes     |
| Red cell indices         | Basophils     |
| Platelet count           | Eosinophils   |

**Urinalysis**

|                  |                    |                         |
|------------------|--------------------|-------------------------|
| Color (optional) | Glucose            | RBC                     |
| Clarity          | Blood              | Hyaline and other casts |
| pH               | Bilirubin          | Bacteria                |
| Specific gravity | Leukocyte esterase | Epithelial cells        |
| Ketones          | Nitrite            | Crystals                |
| Protein          | WBC                | Yeast                   |

**Other Laboratory Tests**

Drug (including cannabis and opioids) and alcohol test  
 Pregnancy test; urine or serum samples, as indicated  
 Follicle-stimulating hormone (FSH) (will be tested in women to confirm postmenopausal status)  
 Erythrocyte sedimentation rate (ESR)  
 Hemoglobin A1c (HbA1c, Glycated hemoglobin)  
 High sensitivity C-reactive protein (hsCRP)

**Abnormal Laboratory Values and Laboratory Adverse Events**

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.4.5.

#### **8.2.4. Drug Concentration and Measurements**

Samples for drug concentration will be collected at visits listed in [Table 1](#). Instructions for blood sample collection will be included in the laboratory manual provided to study sites. [REDACTED]

#### **8.2.5. Anti-Drug Antibody Measurements and Samples**

Samples for ADA measurements will be collected at visits listed in [Table 1](#). Instructions for blood sample collection will be included in the laboratory manual provided to study sites. [REDACTED]

#### **8.2.6. Biomarker, Pharmacodynamic, [REDACTED] and Other Research**

##### **8.2.6.1. Pharmacodynamic and Biomarker Research**

Serum and plasma pharmacodynamic and biomarker samples will be collected at time points according to [Table 1](#). HsCRP will be measured to assess non-specific inflammation. If an increase in hsCRP is observed, other inflammatory cytokines may be measured (eg, ILb, IL6, TNFa, etc.). Alkaline phosphatase will be measured as part of the laboratory testing and, if an increase is observed, bone and collagen markers (CTX-1, P1NP, Osteocalcin, C1M, C3M) may be assessed.

Research assessments may be performed to explore how REGN5069 may modify the perception of pain in patients with pain due to OA of the knee. Pharmacodynamic and biomarker measurements will be performed using the collected samples to determine effects on biomarkers of pain sensation or relevant physiological and pathogenic processes regarding pain and/or pain due to OA. The biomarkers studied may be relevant to the pathophysiology of indication target engagement, mechanism of action of REGN5069, and/or possible toxicities. If necessary, samples may also be used to identify markers associated with AEs.

RNA sequencing (or other methods used to quantitate RNA expression) may be performed on arthroplasty tissue samples collected from any patient who may undergo a joint replacement surgery ([Table 2](#)) to compare the molecular signature of samples from patients treated with REGN5069 relative to placebo. RNA in situ hybridization by RNAscope may also be performed on the tissue samples to measure and localize genes identified in the molecular signature by RNA sequencing and including but not limited to other genes involved in bone metabolism, inflammation, pain, and REGN5069 efficacy and/or safety.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A series of horizontal black bars of varying lengths, likely representing a barcode or a decorative pattern. The bars are arranged in a grid-like structure with some irregular spacing. The lengths of the bars vary significantly, with some being very short and others being very long, creating a dynamic visual effect.

#### **8.2.6.4. Collection of Arthroplasty Tissue Samples (Joint Replacement Surgery Only)**

Tissue samples will be collected at the time of the joint arthroplasty surgery ([Table 2](#)). Detailed procedures for collection, freezing, shipping, and storage of tissue samples will be provided in a separate document.

## **8.2.6.5. Histological Evaluation of Tissue Samples (Joint Replacement Surgery Only)**

A centrally located pathologist will evaluate any slides prepared locally and will oversee processing of tissue shipped in formalin. Hematoxylin and eosin, a basic staining for tissue morphology, will be performed on all samples. Additional stains to be considered include Safranin O/Toluidine blue (stain proteoglycans), Goldner's trichrome (stains collagen fibers), and Alizarin Red S (stains calcium crystals). Immunohistochemistry will be considered but will be limited by the formalin fixation.

### 8.2.6.6. Moticon Digital Insole Device Sub-Study for Gait Assessments

Only study sites selected for participation in the Moticon sub-study for gait assessments using the digital insole device will perform the Moticon-related procedures at the time points according to [Table 1](#). This sub-study will enroll approximately 13 patients per treatment group to obtain

data on at least 10 patients per treatment group for a total of approximately 30 patients across the entire sub-study. For details on these procedures, participating sites will be provided with a Moticon digital insole device manual.

The principle purpose of this sub-study is to assess functional mobility gait parameters as measured by the Moticon insole device in patients with pain due to OA of the knee without an analgesic treatment and in the presence of potential analgesic treatment. The study will also examine correlations of these gait parameters with the WOMAC pain subscale score.

## **9. SAFETY DEFINITIONS, REPORTING, AND MONITORING**

### **9.1. Obligations of Investigator**

The investigator must promptly report to the Institutional Review Board (IRB)/EC all unanticipated problems involving risks to patients, according to local regulations. This may include death from any cause and all serious adverse events (SAEs) related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, according to local regulations.

### **9.2. Obligations of Sponsor**

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IECs/IRBs as appropriate, and to the investigators (in a blinded manner).

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected. Any worsening of or new onset of symptoms related to OA that occur during the screening period prior to study drug administration will be considered expected.

In addition, the sponsor will report in an expedited manner all other SAEs to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the study in the clinical study report to health authorities and IECs/IRB, as appropriate.

### **9.3. Definitions**

#### **9.3.1. Adverse Event**

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

### 9.3.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires inpatient **hospitalization** or **prolongation of existing hospitalization**. Inpatient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE, as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

### 9.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 9.4.3).

### 9.3.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

## 9.4. Recording and Reporting Adverse Events

### 9.4.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of the follow-up period.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

### 9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of the follow-up period or within 226 days of last study drug administration if the patient early terminated from the study - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of the follow-up period/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.
- SAE reported by the patient at the end-of-study phone call and deemed by the investigator to be drug-related will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

### 9.4.3. Other Events that Require Accelerated Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

**Symptomatic Overdose of Study Drug:** Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

**Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 274 days (9 months) of the last dose of study drug. Any

complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

**Adverse Events of Special Interest:** All AESIs, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 9.4.2. No AESIs have been defined for this study.

#### **9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study**

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

#### **9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results**

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the Medical/Study Director in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 9.5.1.

#### **9.4.6. Follow-up**

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

### **9.5. Evaluation of Severity and Causality**

#### **9.5.1. Evaluation of Severity**

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

### **Infusion Reactions**

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

- **Mild:** Mild transient reaction; infusion interruption not indicated; intervention not indicated.
- **Moderate:** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for  $\leq 24$  hours.
- **Severe:** Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

### **9.5.2. Evaluation of Causality**

#### **Relationship of Adverse Events to Study Drug:**

The relationship of AEs to study drug will be assessed by the "blinded" investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by the study drug
- **Related:** There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study drug?

**No:**

- due to external causes such as environmental factors or other treatment(s) being administered

- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

**Yes:**

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after discontinuation of study drug
- reappear or worsen when dosing with study drug
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

**Relationship of Adverse Events to Study Conduct:**

The relationship of AEs to study conduct will be assessed by the blinded investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by study conduct?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by study conduct
- **Related:** There is a reasonable possibility that the event may have been caused by study conduct

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study conduct is provided below. Please note that this list is not exhaustive.

Is there a reasonable possibility that the event may have been caused by the study conduct?

**No:**

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the course of the study
- do not reappear or worsen when dosing with study participation is resumed

**Yes:**

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the course of the study
- resolve or improve after discontinuation from study participation
- reappear or worsen when study participation is resumed

## **9.6. Safety Monitoring**

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

## **9.7. Investigator Alert Notification**

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the reference safety information in the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

# **10. STATISTICAL PLAN**

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked. Analyses related to the Moticon sub-study will not be in the scope of the final SAP.

Analysis variables are listed in Section 4.

## **10.1. Statistical Hypothesis**

The null hypotheses of no treatment difference between a REGN5069 dose and placebo against an alternative hypothesis of some treatment difference in change from baseline to week 12 in WOMAC pain subscale, physical function subscale, and Patient Global Assessment scores will be tested for each dose. Multiplicity adjustment for the 6 null hypotheses will be made using sequentially rejective multiple test procedure to control Type I error rate at 2-sided 0.05 level in the following order:

- H1: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC pain subscale score
- H2: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC pain subscale score
- H3: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC physical function subscale score
- H4: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in WOMAC physical function subscale score
- H5: No treatment difference between 1000 mg REGN5069 and placebo groups in change from baseline to week 12 in Patient Global Assessment score
- H6: No treatment difference between 100 mg REGN5069 and placebo groups in change from baseline to week 12 in Patient Global Assessment score

If at any step a null hypothesis is not rejected, the testing will stop and no further hypothesis in the order will be tested. The details will be provided in the SAP.

## **10.2. Justification of Sample Size**

Up to approximately 240 patients (80 per treatment group) will be randomized to 3 treatment groups in a 1:1:1 allocation. Assuming a standard deviation (SD) of 2.3, 80 patients per treatment group will provide approximately 80% power to detect a treatment difference of 1.1 between the REGN5069 dose and the matching placebo in change from baseline to week 12 in WOMAC pain subscale (using a significance level of 0.05, 2-sided t-test and assuming a dropout rate of 15% [6% due to lack of efficacy or AEs, and 9% due to other reasons]).

## **10.3. Analysis Sets**

### **10.3.1. Efficacy Analysis Sets**

The full analysis set (FAS) will include all randomized patients and will be based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

### **10.3.2. Safety Analysis Set**

The safety analysis set (SAF) will include all randomized patients who received any study drug and is based on the treatment received. Treatment compliance/administration and all safety variables will be analyzed using the SAF.

### **10.3.3. Per Protocol Set**

The per protocol set (PPS) will include all randomized patients who complete the 12-week treatment period and who do not have major protocol deviations through week 12. The PPS will be used for sensitivity analyses for the primary and selected secondary endpoints, as will be defined in the SAP.

#### 10.3.4. Pharmacokinetic Analysis Sets

The PK analysis set will include all treated patients who received any study drug and who had at least 1 non-missing drug concentration measurement following the first dose of study drug.

#### 10.3.5. Anti-Drug Antibody Analysis Sets

The ADA analysis set will include all treated patients who received any study drug and who had at least 1 non-missing ADA result following the first dose of study drug.

### 10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

#### 10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set (eg, FAS, provided in Section 10.3)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

#### 10.4.2. Demography and Baseline Characteristics

Baseline demographic, disease characteristics, and exposure to study drug will be summarized descriptively by treatment groups using descriptive statistics. Continuous variables will be summarized with mean, median, and SD, minimum, and maximum. Categorical variables will be summarized with counts and percentages.

#### 10.4.3. Efficacy Analyses

##### 10.4.3.1. Primary Efficacy Analysis

The primary estimand for the primary objective is the difference in means between both REGN5069 dose + protocol-defined rescue medication and placebo + protocol-defined rescue medication in the change from baseline to week 12 in the WOMAC pain subscale score of patients in the FAS. All collected data will be included in the analysis regardless of whether prohibited medication was taken. Missing values will be imputed with the multiple imputation

approach, where intermediate missing data will be first imputed using the Markov Chain Monte Carlo method and then the remaining missing data with a monotone missing pattern will be imputed with a regression method. The regression model will adjust for treatment, randomization strata, and baseline score. For patients who drop out due to lack of efficacy or AEs, each imputed value will be further adjusted by subtracting the mean change from baseline to the respective post-baseline time point calculated from patients in the same treatment group with observed data at that time point. For each complete dataset, the primary efficacy endpoint of change from baseline to week 12 in WOMAC pain subscale score will be analyzed using analysis of covariance (ANCOVA) model which will include treatment, randomization strata, and baseline score as covariate. The least-squares means estimates, as well as the difference of the estimates between each dose and placebo with standard error, p-values, and 95% confidence intervals will be provided by combining results from the analyses of the multiple imputed datasets using Rubin's formulae. Further details will be provided in the SAP.

#### 10.4.3.2. Secondary Efficacy Analysis

The continuous secondary endpoints will be analyzed similarly as specified in Section 10.4.3.1.

For the analyses of categorical secondary endpoints, the Cochran-Mantel-Haenszel test stratified by the K-L category (2-3 vs 4) will be used with missing data considered as non-response. The continuous secondary endpoints will be analyzed similarly as specified in Section 10.4.3.1.

#### 10.4.4. Safety Analysis

The safety data including TEAEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG) will be summarized by treatment groups.

Thresholds for potentially clinically significant values (PCSVs) in laboratory parameters and vital signs will be defined by the sponsor and be in effect at the time of the final SAP approval.

##### 10.4.4.1. Adverse Events

###### Definitions

For safety variables, 3 observation periods are defined:

- The **pre-treatment period** is defined as the time from signing the ICF to before the first dose of study drug.
- The **treatment period** is defined as the day from first dose of study drug to the last dose of study drug + 4 weeks (week 12)
- The **post-treatment period** is defined as the time after the treatment period (after week 12).

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment period.

###### Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.5.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

#### 10.4.4.2. Other Safety

##### Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

##### Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a PCSV at any post-randomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out-of-laboratory range values.

##### Imaging

Change from baseline (ie, screening visit) in joint space width of the knees and hips will be summarized by treatment group over time. The number and percentages with images requiring arthropathy adjudication, as well as the number and percentage of patients with confirmed adjudicated arthropathy, will be summarized by treatment group. Patient listings of cases confirmed by adjudication will also be provided.

#### 10.4.4.3. Treatment Exposure

Because of the half-life of the biologic being studied, the duration of exposure (in days) during the study will be presented by treatment group and calculated as:

- (Date of last administration of study drug - date of the first study drug administration after randomization) + 28

The number and percentage of patients randomized and exposed to double-blinded study drug will be presented by specific time period for each treatment group. The time periods will be specified in the final SAP.

#### 10.4.4.4. Treatment Compliance

Overall treatment compliance is defined as the actual dose administered compared to the prescribed dose of treatment during the treatment phase up to treatment discontinuation. It is calculated according to the following formula:

$100 * \text{total dose administered} / \text{prescribed dose}$ .

The total number of doses will be summarized by treatment groups.

#### 10.4.5. Pharmacokinetics

##### 10.4.5.1. Analysis of Drug Concentration Data

Summaries of trough concentrations ( $C_{\text{trough}}$ ) of functional REGN5069 will be presented by nominal time point and dose. Plots of individual  $C_{\text{trough}}$  will be presented by actual day (linear and log scales). Plots of mean and median  $C_{\text{trough}}$  will be presented by nominal day (linear and log scale).

##### 10.4.5.2. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Population PK and exposure-response analyses for biomarkers, efficacy, and safety endpoints may be performed, as appropriate, and presented in separate reports.

#### 10.4.6. Analysis of Anti-Drug Antibody Data

Listings of ADA positivity and titers presented by patient, time point, and treatment group will be provided. Prevalence of treatment-emergent and treatment-boosted ADA response will be assessed as absolute occurrence (N) and percent of patients (%), grouped by treatment group. Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADAs on safety may be provided.

Anti-drug antibody parameters include status (positive or negative) and titer as follows:

- Treatment emergent - defined as any post-dose ADA positive response when baseline results are negative or missing.
- Treatment boosted - defined as any post-dose ADA response that is at least 9-fold over baseline titer levels when baseline results are positive
- Titer values
- Titer category for patients, by patient's maximal titer value:
  - Low (titer < 1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer > 10,000)

#### 10.5. Interim Analysis

No formal interim analysis is planned for the study. The unblinded primary efficacy analysis will be conducted when 12-week data are available for all randomized patients. No individual treatment assignments will be unblinded to personnel directly involved with the conduct of the

study until after the final database lock. The unblinded summarized results based on 12-week data will be disclosed.

## 10.6. Additional Statistical Data Handling Conventions

General rules for handling missing data:

- Rules for handling missing data for efficacy assessments will be provided in the final SAP
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study drug, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study drug date, then the start date by the study drug intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

Unscheduled assessments:

- Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

## 10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

# 11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

## 11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study, including data validation will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool called Medidata RAVE.

## **11.2. Electronic Systems**

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Patient diary
- Moticon wearable insole device (for use at selected sites only)

## **12. STUDY MONITORING**

### **12.1. Monitoring of Study Sites**

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### **12.2. Source Document Requirements**

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible for ensuring quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

### **12.3. Case Report Form Requirements**

Study data obtained during the course of the clinical study will be recorded on electronic CRFs within the EDC system by trained site personnel. All required CRFs must be completed for each patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for

each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

### **13. AUDITS AND INSPECTIONS**

This study may be patient to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

### **14. ETHICAL AND REGULATORY CONSIDERATIONS**

#### **14.1. Good Clinical Practice Statement**

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

#### **14.2. Informed Consent**

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

### **14.3. Patients Confidentiality and Data Protection**

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

### **14.4. Institutional Review Board/Ethics Committee**

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

#### **14.5. Clinical Study Data Transparency**

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site after the study results are posted on a clinical trial registry.

### **15. PROTOCOL AMENDMENTS**

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local regulations regulatory authority, approval will also be sought.

### **16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE**

#### **16.1. Premature Termination of the Study**

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

#### **16.2. Close-out of a Site**

The sponsor and the investigator have the right to close-out a site prematurely.

##### **Investigator's Decision**

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

##### **Sponsor's Decision**

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time

- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

## 17. STUDY DOCUMENTATION

### 17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF that will be provided to the sponsor.

### 17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

## 18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

#### Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

#### Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13).

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All patient data collected during the study will be recorded on paper or electronic CRFs unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRF (Section 12.3 and Section 17.1).

### **Study Documentation**

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

## **19. CONFIDENTIALITY**

Confidentiality of information is provided as a separate agreement.

## **20. FINANCING AND INSURANCE**

Financing and insurance information is provided as a separate agreement.

## **21. PUBLICATION POLICY**

Publication rights and procedures will be outlined in a separate clinical study agreement.

## **22. REFERENCES**

Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29(8):1039-49.

Baloh RH, Gorodinsky A, Golden JP, Tansey MG, Keck CL, Popescu NC, et al. GFRalpha3 is an orphan member of the GDNF/neurturin/persephin receptor family. Proc Natl Acad Sci U S A 1998a; 95(10):5801-6.

Baloh RH, Tansey MG, Lampe PA, Fahrner TJ, Enomoto H, Simburger KS, et al. Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRalpha3-RET receptor complex. *Neuron* 1998b; 21(6):1291-302.

Baudet C, Mikaelson A, Westphal H, Johansen J, Johansen TE, Ermfors P. Positive and negative interactions of GDNF, NTN and ART in developing sensory neuron subpopulations, and their collaboration with neurotrophins. *Development* 2000; 127(20):4335-44.

Bespalov MM, Saarma M. GDNF family receptor complexes are emerging drug targets. *Trends Pharmacol Sci* 2007; 28(2):68-74.

Centers for Disease Control and Prevention. <https://www.cdc.gov>. Published Updated Accessed

Ceyhan GO, Bergmann F, Kadihasanoglu M, Erkan M, Park W, Hinz U, et al. The neurotrophic factor artemin influences the extent of neural damage and growth in chronic pancreatitis. *Gut* 2007; 56(4):534-44.

Deshpande BR, Katz JN, Solomon DH, Yelin EH, Hunter DJ, Messier SP, et al. Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. *Arthritis Care Res (Hoboken)* 2016; 68(12):1743-50.

Durbec P, Marcos-Gutierrez CV, Kilkenny C, Grigoriou M, Wartiovaara K, Suvanto P, et al. GDNF signalling through the Ret receptor tyrosine kinase. *Nature* 1996; 381(6585):789-93.

Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society clinical rating system. *Clin Orthop Relat Res* 1989; 248):13-4.

Jing S, Yu Y, Fang M, Hu Z, Holst PL, Boone T, et al. GFRalpha-2 and GFRalpha-3 are two new receptors for ligands of the GDNF family. *J Biol Chem* 1997; 272(52):33111-7.

Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. *Rheumatology (Oxford)* 2014; 53(5):937-47.

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58(1):26-35.

Mabbott NA, Baillie JK, Brown H, Freeman TC, Hume DA. An expression atlas of human primary cells: inference of gene function from coexpression networks. *BMC Genomics* 2013; 14(632).

Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A* 2014; 111(14):5147-52.

Maiese K. Picking a bone with WISP1 (CCN4): new strategies against degenerative joint disease. *J Transl Sci* 2016; 1(3):83-5.

Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. *Nat Rev Rheumatol* 2013; 9(11):654-64.

Murota H, Izumi M, Abd El-Latif MI, Nishioka M, Terao M, Tani M, et al. Artemin causes hypersensitivity to warm sensation, mimicking warmth-provoked pruritus in atopic dermatitis. *J Allergy Clin Immunol* 2012; 130(3):671-82.e4.

Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A* 2014; 111(14):5153-8.

Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *Jama* 2013; 310(6):591-608.

Naveilhan P, Baudet C, Mikaelson A, Shen L, Westphal H, Ernfors P. Expression and regulation of GFRalpha3, a glial cell line-derived neurotrophic factor family receptor. *Proc Natl Acad Sci U S A* 1998; 95(3):1295-300.

Network EMCSAI. 2012 Musculoskeletal Health in Europe: Report v5.0. Vol. 5(Issue).

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117(2):391-7.

Shinoda M, Takeda M, Honda K, Maruno M, Katagiri A, Satoh-Kuriwada S, et al. Involvement of peripheral artemin signaling in tongue pain: possible mechanism in burning mouth syndrome. *Pain* 2015; 156(12):2528-37.

Treanor JJ, Goodman L, de Sauvage F, Stone DM, Poulsen KT, Beck CD, et al. Characterization of a multicomponent receptor for GDNF. *Nature* 1996; 382(6586):80-3.

Trupp M, Scott R, Whittemore SR, Ibanez CF. Ret-dependent and -independent mechanisms of glial cell line-derived neurotrophic factor signaling in neuronal cells. *J Biol Chem* 1999; 274(30):20885-94.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380(9859):2163-96.

Worby CA, Vega QC, Chao HH, Seasholtz AF, Thompson RC, Dixon JE. Identification and characterization of GFRalpha-3, a novel Co-receptor belonging to the glial cell line-derived neurotrophic receptor family. *J Biol Chem* 1998; 273(6):3502-8.

Yang X, Ambrogelly A. Enlarging the repertoire of therapeutic monoclonal antibodies platforms: domesticating half molecule exchange to produce stable IgG4 and IgG1 bispecific antibodies. *Curr Opin Biotechnol* 2014; 30(225-9).

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007; 15(9):981-1000.

**23. INVESTIGATOR'S AGREEMENT**

I have read the attached protocol: A Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Efficacy and Safety of REGN5069 in Patients with Pain due to Osteoarthritis of the Knee and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

---

(Signature of Investigator)

---

(Date)

---

(Printed Name)

**SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS**

**(Medical/Study Director, Regulatory Representative, Clinical Study Leader, and Biostatistician)**

*To the best of my knowledge, this report accurately describes the conduct of the study.*

Study Title: A Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Efficacy and Safety of REGN5069 in Patients with Pain due to Osteoarthritis of the Knee

Protocol Number: R5069-OA-1849

Protocol Version: R5069-OA-1849 Amendment 1

*See appended electronic signature page*

Sponsor's Responsible Medical/Study Director

*See appended electronic signature page*

Sponsor's Responsible Regulatory Liaison

*See appended electronic signature page*

Sponsor's Responsible Clinical Study Leader

*See appended electronic signature page*

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00083543 v1.0

ESig Approval



ESig Approval



ESig Approval



ESig Approval



Signature Page for VV-RIM-00083543 v1.0 Approved