STATISTICAL ANALYSIS PLAN
VERSION 2

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
Protocol Number:	R5069-OA-1849
Clinical Phase:	Phase 2
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Accelerated arthropathy
DA	Destructive arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CPK	Creatine phosphokinase
ECG	Electrocardiogram
EDC	Electronic data collection system
EOS	End of study
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRT	Interactive response technology
IWRS	Interactive web response system
K-L	Kellgren-Lawrence
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PT	Preferred term
QTcF	QT interval with Fridericia's correction
Q4W	Every 4 weeks
RBC	Red blood cell
SAE	Serious adverse event

SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1. OVERVIEW

The purpose of the Statistical Analysis Plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the definitions and statistical methods to be used in the analysis of data for study R5069-OA-1849.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued prior to the first step database lock and before unblinding of the study.

Due to public health measures implemented to address the world-wide COVID-19 pandemic, some sites may suspend onsite study visits or patients may opt not to attend. The handling of missing data and analyses related to COVID-19 are specified through the SAP and summarized in Section 9. There is, however, expected to be no impact on missing data at the Week 12 WOMAC data due to COVID-19 mitigations of remote data collection.

1.1. Background/Rationale

This is a multicenter, Phase 2, randomized, double-blind, multi-dose, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of REGN5069 in patients with pain due to osteoarthritis (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 non-steroidal anti-inflammatory drugs (NSAIDs) (eg, prescription NSAIDs or over the counter NSAIDs at or near prescription doses), and opioid therapy or unavailability of opioid therapy.

1.2. Study Objectives

1.2.1. Primary Objectives

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.

1.2.2. 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

1.2.3. 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, for a subset of patients, 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

1.2.4. Modifications from the Statistical Section in the Final Protocol

1.2.4.1. SAP Version 1.0

SAP V1.0 is based on Protocol R5069-OA-1849 Amendment 1. The following were modified or were not specified in the protocol but are clarified/added in the SAP V1.0.

Table 1: SAP Version 1 Modifications from Final Protocol Amendment PA1

Item no.	Issue Addressed	Protocol Amendment 1 Text	SAP V1 Clarification or Addition
1.	In order to be in compliance with SOP-CTM2620 Protocol Deviations Management, the terminology for PD classification changed, from *minor and major*, to *minor and important*.		
2.	The Per Protocol analysis set definition is clarified, as not all major/important PDs are to produce exclusions from PP.	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.	The per protocol set (PPS) includes all randomized patients who complete the 12-week treatment period and who do not have *relevant* protocol deviations (PDs) through week 12. The PPS is to be used for sensitivity analyses for the primary and selected secondary endpoints. The relevant PDs are defined as a subset of the important PDs in Appendix 11.4.
3.	The statistical model used for categorical analyses: randomization strata is clarified as only the KL-score to be used besides baseline endpoint score.	The regression model will adjust for treatment, randomization strata, and baseline score.	"… is to be analyzed using a MMRM with terms for baseline WOMAC Pain subscale score, randomization strata (K-L category [2 to 3, or 4]), treatment, visit, and treatment-by-visit interaction as fixed effects."

Item no.	Issue Addressed	Protocol Amendment 1 Text	SAP V1 Clarification or Addition
4.	The statement on planned interim analysis is clarified	**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. and: **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.	**7. Interim Analysis** No interim analysis for the purpose of early study-termination is planned for the study. The unblinded primary efficacy analysis will be conducted when all randomized patients have been followed for 12 weeks after the first dose of study medication. The unblinded summarized results based on 12-week data is to be disclosed to the study team. No individual treatment assignments will be unblinded to personnel directly involved with the conduct of the study until after the final database lock.
5	Subgroup analysis by geographic region was added for demographics and baseline characteristics, use of rescue and prohibited medication, and efficacy.		

Item no.	Issue Addressed	Protocol Amendment 1 Text	SAP V1 Clarification or Addition
6	Study Observation periods are clarified	**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).	**Study Observation Period –** Unless otherwise stated, analysis of all safety and non-safety variables captured at multiple visits are to be analyzed by the following observations periods: • *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 days from first dose of study drug to the day of last dose + 28 days (4 weeks). Summaries for the Treatment Period are based on the SAF. • *The Follow-Up Period* is defined from the end of the Treatment Period to the Week 36 Visit/Early Termination Visit, regardless of the patient having completed the treatment period (week 12 visit) or not. • *The Post-Follow-Up Period* is defined from the end of the Follow-Up Period to the phone call/Early Termination Visit.
7.	COVID-19 mitigation as per regulatory guidance	These were not described in the protocol.	Missing data handling and analyses related to COVID-19 are specified in the SAP.

Item no.	Issue Addressed	Protocol Amendment 1 Text	SAP V1 Clarification or Addition
8.	Some sensitivity analyses and supportive efficacy variables are added.	1. Protocol-defined exploratory endpoint: 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 2. Secondary supportive variables that were not described in the protocol.	1. The exploratory endpoint area under the curve for WOMAC pain subscale score is being replaced with the following two supportive primary endpoint analyses: • WOMAC pain subscale scores averaged across Weeks 4, 8, and 12. • WOMAC pain subscale scores averaged across Weeks 8 and 12. The same method as for the primary endpoint will be used for handling missing data 2. Secondary Supportive variables Other timepoints of interest are Week 16, 24 and 36. • Change in WOMAC pain subscale scores from baseline to week 16, 24, 36 • Change in WOMAC physical function subscale scores from baseline to week 8, 16, 24, 36 • Change in WOMAC stiffness subscale scores from baseline to week 8, 16, 24, 36 • Change in WOMAC Total subscale scores from baseline to week 8, 16, 24, 36 • Change in the PGA scores from baseline to week 8, 16, 24, 36 The following supportive variables are included in order to assess duration of treatment effect: • Change in WOMAC pain subscale scores from week 12 to week 24 and 36 • Change in WOMAC physical function subscale scores week 12 to week 24 and 36

Item no.	Issue Addressed	Protocol Amendment 1 Text	SAP V1 Clarification or Addition
			• Change in WOMAC stiffness subscale scores from week 12 to week 24 and 36 • Change in WOMAC Total subscale scores from week 12 to week 24 and 36 • Change in the PGA scores from week 12 to week 24 and 36
		3. COVID-19 mitigation that was not described in the protocol	3. COVID-19 mitigation A sensitivity analysis will be performed excluding data collected via telephone, using the same method as for the primary endpoint 12-weeks analysis.
9.	Decision on analyzing bone-specific laboratory results will be made independent of the condition described in the protocol.	Conditional endpoints: if a mean 10% increase in alkaline phosphatase is observed at week 4, CTX-1, P1NP, Osteocalcin, C1M, and C3M are to be measured and change from baseline to week 12 are exploratory endpoints	CTX-1, P1NP, Osteocalcin, C1M, and C3M may be measured and change from baseline to week 12 would be analyzed as exploratory endpoints. If analyzed, there will be a separate analysis plan and report.

1.2.4.2. SAP Version 2.0

In this section we summarize the modifications to the original SAP V1.0, as presented in this current version of SAP (V2.0).

After reviewing the interim analysis data from the Phase 2 clinical study (R5069-OA-1849), Regeneron has concluded that the week 12 data did not show significance between the placebo and each of the REGN5069 treatment arms in the WOMAC pain subscale score as well as other efficacy parameters evaluated. Additionally, there were no new safety findings or concerns associated with REGN5069. Based on the failure to demonstrate additional benefit in the REGN5069 dose groups compared to placebo, Regeneron made the decision to discontinue REGN5069 in the OA pain indication. The Phase 2 study (R5069-OA-1849) will be prematurely terminated after all patients have completed the Week 36 visit (visit 10) and will not be required to complete the Week 52 phone call, specified in Schedule of Events (Protocol Amendment 1, Section 8.1).

An abbreviated CSR will now be produced for this study, and this SAP amendment describes analysis changes stemming from this decision.

Table 2 presents the details of these changes from SAP Version 1.0.

Table 2: SAP Version 2.0 Modifications from SAP Version 1.0

Sections Changed	Changes and Rationale
Section 2.3 Study Plan	**Inserted:** As the Interim Analysis showed no treatment effect, and there were no safety signals observed, it was decided to terminate the study at the time last patient completes week 36 visit; thus, a limited number of study patients will have completed week 52 phone call.
	Rationale: The Interim Analysis showed no treatment effect, and there were no safety signals observed, thus the PA1 study extension to 52 weeks is no further necessary.
Section 3.2 Analysis Datasets, Per Protocol Set	**Deleted Section 3.2**
	Rationale: As the Interim Analysis showed no treatment effect, the sensitivity analyses are no further necessary. Per Protocol Set analysis was intended as sensitivity analysis, thus defining this analysis set is no further necessary.

Sections Changed	Changes and Rationale
Section 4.4.2.1 Supportive analyses	**Deleted:** Further supportive analyses will be performed, using estimands at other timepoints of interest than Week 12 (Week 16, 24 and 36). • Change in WOMAC pain subscale scores from baseline to week 16, 24, 36 • Change in WOMAC physical function subscale scores from baseline to week 8, 16, 24, 36 • Change in WOMAC stiffness subscale scores from baseline to week 8, 16, 24, 36 • Change in WOMAC Total subscale scores from baseline to week 8, 16, 24, 36 • Change in the PGA scores from baseline to week 8, 16, 24, 36 The following supportive variables are included in order to assess duration of treatment effect: • Change in WOMAC pain subscale scores from week 12 to week 24 and 36 • Change in WOMAC physical function subscale scores week 12 to week 24 and 36 • Change in WOMAC stiffness subscale scores from week 12 to week 24 and 36 • Change in WOMAC Total subscale scores from week 12 to week 24 and 36 • Change in the PGA scores from week 12 to week 24 and 36
	Rationale: As the Interim Analysis showed no treatment effect, these supportive analyses are no further necessary.
Section 4.5.12 Joint Replacement	**Inserted:** As the study will now end when the last patient completes the week 36 visit, the week 52 phone call will not be performed for most of the patients; all available Joint Replacement information will be summarized in a listing.
	Rationale: Provided clarification on the collection and reporting of information on joint replacement**.**

Sections Changed	Changes and Rationale
Section 4.5.3 Exploratory Variables	**Deleted:** Changes in CTX-1, P1NP, Osteocalcin, C1M, and C3M from baseline to week 12 may also be measured and analyzed, pending further decisions.
	Rationale: As the Interim Analysis showed no treatment effect, and there were no safety signals observed, these exploratory analyses are no further necessary.
Section 5.3 Rescue medication	**Change from:** Analogous analyses are to be performed for the Follow-up Period.
	Change to: Analogous analyses are to be performed for the Follow-up Period, up to Week 24 visit. Rescue medication inadvertently collected in the diary past Week 24 (e.g. due to missing visits because of COVID-19 pandemic) will be censored and not included in the outputs.
	Rationale: The protocol-planned rescue medication collection is limited to up to Week 24 visit. Due to COVID-19, a few patients missed this visit or completed it remotely, and continued to complete the rescue medication diary past Week 24. As this information is to be collected as concomitant medication past week 24, it will be reported only as such.
Section 5.7.1.1 Sensitivity analysis	**Deleted** Section 5.7.1.1
	Rationale: As the Interim Analysis showed no treatment effect, the sensitivity analyses (that were not already performed at IA time) are no further necessary.

Sections Changed	Changes and Rationale
Section 5.7.1.3 Subgroup analyses	**Change from:** Age groups [< 65, >= 65-74, ≥ 75 years] Forest plots for the subgroup analysis are to be provided.
	Change to: Age groups [< 65, >= 65] Forest plots for the subgroup analysis are to be provided for all above subgroups for the primary endpoint. Summaries and plots by visit are to be provided for the primary endpoint and secondary endpoints of physical function subscale score and PGA by K-L category and geographic region.
	Rationale: The number of patients >=75 is too small for the model to converge. Also provided a clarification on how the subgroup analysis will be presented.
Section 5.8.1 Adverse Events	**Inserted:** • All TEAEs by SOC, PT, relationship • All AEs by SOC, PT • All SAEs, by study period • All SAEs by severity and study period • All SAEs by relationship, treatment and follow-up period Follow-up AEs will be summarized similarly as TEAEs, as well as AEs occurring during Treatment and Follow-up Periods combined. • Listing of TEAEs leading to infusion interruption
	Rationale: Provided further clarification on the AE analyses to be performed.
Section 5.8.1 Adverse Events	**Deleted:** • Non-serious TEAEs by SOC and PT • All Joint replacements
	Rationale: As at the IA there were no safety issues detected, there is no further need to summarize non-serious AEs separately. All AEs and Serious AEs summaries suffice. Also, joint replacement was performed for a single patient, so a summary table is no further necessary, all information collected will be presented in the joint replacement listing.

Sections Changed	Changes and Rationale
Section 5.8.2 Clinical Laboratory Measurements	**Deleted:** 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.
	Inserted: For all analytes, plots of change from baseline by visit are to be presented by treatment group.
	Rationale: As at the IA there were no safety issues detected, the PCSV analysis is sufficient, shift tables are no further necessary. Also provided clarification on what figures will be presented for laboratory data.
Appendix 11.2 Reference for Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)	**Deleted** Conjugated Bilirubin ALT/AST and Total Bilirubin ALT/AST and Total Bilirubin and ALP Total Cholesterol Triglycerides
	Rationale: As at the IA there were no safety issues detected, these PCSVs were not of further interest.
Appendix 11.2 Reference for Criteria for … PCSV	**Deleted** HbA1c
	Rationale: This analyte was only to be collected at baseline, so no PCSV analysis is to be performed.
Appendix 11.4 Per Protocol Exclusions	**Deleted Appendix 11.4**
	Rationale: As the PPS sensitivity analysis is no further being performed, the list of protocol deviations leading to PPS exclusion is not further necessary.

1.2.5. Revision History for SAP Amendments

Original SAP Version 1.0 was finalized on 29 May 2020 and was based on Protocol Amendment 1.

Revised SAP Version 2.0 is revised as summarized in Section 1.2.4.2 above.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a multicenter, Phase 2, multicenter, randomized, double-blind, multi-dose, parallel-arm, placebo-controlled study designed to evaluate the safety and efficacy of REGN5069 in patients with pain due to osteoarthritis of the knee. Up to approximately 240 patients are 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, for a total of 3 doses Q4W during the 12-week treatment period.

Randomization is 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. The index knee joint is defined as the knee joint affected by OA and selected for primary assessment for this study.

An independent Data Monitoring Committee (IDMC) is monitoring unblinded data. 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 is to determine if these or other actions should be taken.

2.2. Sample Size and Power Considerations

Up to approximately 240 patients (80 per treatment group) are randomized to 3 treatment groups in a 1:1:1 allocation. Assuming a standard deviation (SD) of 2.3, 80 patients per treatment group provides 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 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score (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]).

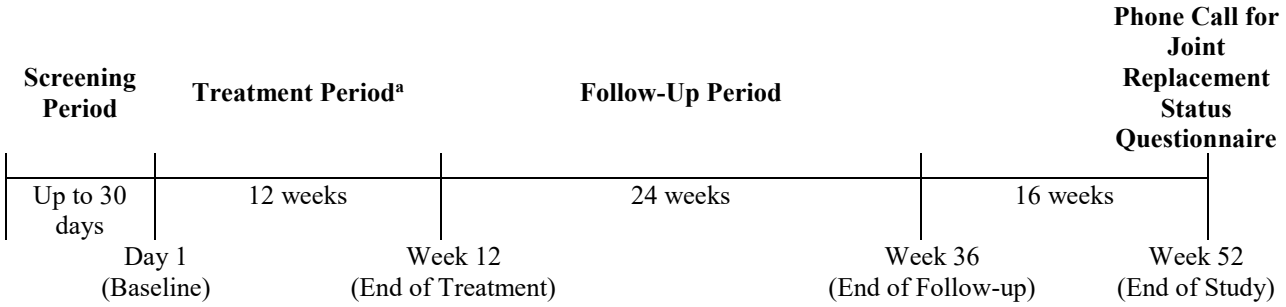
The WOMAC index is comprised of 24 parameters grouped in subscales (pain, physical function, stiffness) and is reported using a Numerical Rating Scale score of 1-10.

2.3. Study Plan

The study was intended to consist 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 was 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 was to be enrolled in the study for approximately 56 weeks, including the screening period and the period up to the end-of-study phone call.

As the Interim Analysis showed no treatment effect, and there were no safety signals observed, it was decided to terminate the study at the time last patient completes week 36 visit; thus, a limited number of study patients will have completed week 52 phone call.

Figure 1: Study Flow Diagram



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

The Schedule of Events table is presented in Appendix 11.1, Table 3 .

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations are used for all statistical analyses:

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all randomized patients and is based on the treatment allocated (as randomized). Efficacy endpoints are analyzed using the FAS.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized patients who received any study drug and is based on the treatment received (as treated). Treatment compliance/administration and all safety variables are analyzed using the SAF.
Determination of "as treated" is done as follows:

- Patients randomized to the placebo arm who receive at least one dose of active REGN5069 1000mg will be considered as treated with REGN5069 1000mg.
- Patients randomized to the placebo arm who receive at least one dose of active REGN5069 100mg and no dose of REGN5069 1000mg will be considered as treated with REGN5069 100mg.
- Patients randomized to any of the REGN5069 arms that did not receive any dose of either REGN5069 1000mg or 100mg will be considered as treated with placebo and classified in the placebo treatment arm for the purpose of analysis using the SAF.

3.3. The Pharmacokinetic Analysis Set

The PK analysis set includes 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. Patients are analyzed according to the treatment actually received (as treated).

3.4. The Immunogenicity Analysis Set

The anti-drug antibody (ADA) analysis set (AAS) includes all treated patients who received any study drug and had at least one non-missing ADA result from the REGN5069 ADA assay after the first dose of study drug. Patients will be analyzed according to the treatment actually received**.**

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristic variables are to be summarized by treatment group:

- Age at screening (years)
- Age category (<65, >=65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Baseline Weight(kg)
- Baseline Height(cm)
- Baseline Body mass index (BMI) calculated from weight and height
- K-L screening score of index knee, as per the electronic data collection system (EDC) (and by the integrated response system (IRT) if different)
- Subjects participating in the MOTICON sub-study
- WOMAC pain subscale at baseline.
- Geographic region: USA, MGU (Republic of Moldova, Georgia, Ukraine), and Poland
- Duration of OA at baseline
- Walking aid use at baseline
- History of analgesic intolerance and inadequate pain relief

4.2. Medical History

Medical history was recorded at screening and is to be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23 or later.

4.3. Prior/Concomitant Medications and Procedures

Prior medication and procedures were collected at the screening visit as medication and procedure history. Any treatment administered and/or procedures performed from screening to the end of the follow-up period is 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. These are to be analyzed as per the study observation periods defined in Section 5.

Medications are coded to the Anatomical Therapeutic Chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to WHO Drug Dictionary (WHODD) Version REGENERONWHOB3Global202003 or higher. Patients are counted once in all ATC categories linked to the medication.

Medication/Procedure Classifications

Prior medications/procedures are defined as medications administered and/or procedures performed starting prior to the patient signing the informed consent form (ICF).

Pre-treatment concomitant medications/procedures are defined as medications administered and/or procedures performed starting as follows:

On-treatment concomitant medications/procedures are defined as any treatment administered and/or procedures performed after the administration of first dose until 28 days after administration of last dose.

Follow-Up concomitant medications/procedures are defined as medications administered and/or procedures performed after the on-treatment period, and up to Week 36 Visit.

- for opioids, the pre-treatment period is defined as starting 4 weeks before ICF
- for genicular nerve block and any other similar procedures, it is defined starting 3 months before ICF
- for the rest of concomitant medications/procedures, starting on or after the patient signing the informed consent form (ICF)

and until before the first dose of study drug

4.3.1. Rescue Medication and Prohibited Medication and Procedures During the Study

Rescue Medication

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 are being 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 are to be dispensed to patients as rescue medication. In the event that pain relief for OA pain is inadequate, patients are to 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.

Prohibited Medication and Procedures

Patients are 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. 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 infusions
- 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 in the protocol for permitted muscle relaxants)
- Corticosteroids (topical, intranasal, and inhaled formulations are permitted), adrenocorticotropic hormone
- Cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus (topical tarcolimus 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)

The list of concomitant medications taken by study patients is reviewed by the study team to determine if any medication falls under one of the above categories. If a concomitant medication is adjudicated to be prohibited, a protocol deviation is recorded.

The following variables are to be summarized for prohibited medications, overall and by geographical region:

- Use of at least one prohibited medication during Pre-treatment Period, Treatment Period, and Follow-up Period.
- Use of any prohibited medications, as well as selected prohibited medications (NSAIDs, opioids and corticosteroids), by visit.
- Receiving prohibited procedures during Pre-treatment Period, Treatment Period, and Follow-up Period.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

The primary endpoint of the study is the change from baseline to week 12 in the WOMAC pain subscale score.

The WOMAC index is comprised of 24 parameters grouped 3 in subscales (pain, physical function, and stiffness) and is reported using a Numerical Rating Scale score of 1-10.

4.4.2. Secondary Efficacy Variables

The secondary efficacy endpoints of the study are:

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

The Patient Global Assessment of OA (PGA) 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).

4.4.2.1. Supportive variables

The following two supportive endpoints are to be analyzed instead of the exploratory area under the curve endpoint:

- WOMAC pain subscale scores averaged across Weeks 4, 8, and 12.
- WOMAC pain subscale scores averaged across Weeks 8 and 12.

4.4.3. Exploratory Efficacy Variables

The exploratory efficacy endpoints of the study are:

- The exploratory endpoint described in the protocols as "Area under the curve for WOMAC pain subscale score (for the 12-week treatment period)" is being replaced by supportive endpoints described in section 4.4.2.1.
- Change in gait and functional mobility parameters recorded by a wearable insole device from baseline to week 12 in a subset of patients at participating sites.

4.5. Safety Variables

Patient safety is assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG, neurological exams and physical exams. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study drug.

4.5.1. Adverse Events and Serious Adverse Events

Adverse event information is to be collected until the patient's last study visit. Serious adverse event information is to be collected until the event is considered chronic and/or stable and/or resolved.

Adverse events (AE) and Serious Adverse Events (SAE) are collected from the time of informed consent signature and then at each visit until the end of follow-up visit (week 36) for AEs and until end of study visit (week 52) for SAEs. All AEs are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the MedDRA® (the latest current available version).

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. Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

An SAE is an AE that is classified as serious according to the criteria specified in the protocol. SAEs 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 is to be reported to the sponsor. SAEs 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 are to be reported to the sponsor. SAEs reported by the patient at the end-of-study phone call and deemed by the investigator to be drug-related are to be reported to the sponsor.

4.5.2. Safety Variables (Secondary Study Endpoints)

The secondary safety endpoints of the study are:

- The incidence of treatment-emergent adverse events (TEAEs) throughout the study duration
- The incidence of imaging abnormalities consistent with accelerated arthropathies as assessed by X-ray and MRI throughout the study duration
- Presence of anti-REGN5069 antibody development throughout the study duration

4.5.3. Exploratory Safety Variables

Exploratory safety endpoints include:

- Change in high sensitivity C-reactive protein (hsCRP) from baseline to week 12
- Change in alkaline phosphatase from baseline to week 12

4.5.4. Adverse Events of Special Interest

No AESIs have been defined for this study.

4.5.5. Acute Intravenous 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 and graded using the grading scales as instructed in the protocol.

4.5.6. Laboratory Safety Variables

The clinical laboratory tests include blood chemistry, hematology, urinalysis, urine chemistries, hs-CRP, and others. Samples for laboratory testing are to be collected at the time points specified in the Schedule of Events (Table 3). Clinical laboratory values are in standard international (SI) units, including associated normal ranges provided by the central laboratory, and grouped by function in summary tables. Clinical laboratory values in conventional (US) units are also to be available in the database, with associated normal ranges. For laboratory measurements performed at local laboratories, the corresponding local laboratory normal ranges will be used.

Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) are used in central lab result summaries. Potentially clinically significant values (PCSV) ranges are to be applied to central lab test values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.7. Vital Signs

The following vital signs parameters are to be collected according to the Schedule of Events in Table 3:

- Body temperature (°C)
- Semi-recumbent/2-minute standing systolic and diastolic blood pressures (mmHg) and heart rate (bpm)
- Respiratory rate (bpm)

Both actual values and "change from baseline" values (defined as the post-baseline value minus the baseline value) are to be used in the result summaries. Potentially clinically significant values (PCSV) ranges are to be applied to the vital sign parameter values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.8. Orthostatic Hypotension

A patient is to be determined to have orthostatic hypotension if any of the following criteria are met:

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

OR

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

OR

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

OR

- The patient is unable to stand for standing blood pressure measurements due to dizziness or lightheadedness

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

4.5.9. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG is to be performed according to the Schedule of Events in Table 3 with the patient in the semi-recumbent position for approximately 10 minutes and prior to blood samples being drawn. Heart rate is recorded from the ventricular rate and the PR/PQ, QRS, and QT, QTcF intervals, and ECG status (normal, abnormal not clinical significant or abnormal clinical significant) is also recorded.

QTcF is defined as follows:

$$QTcF\ (ms) = QT/RR^{1/3},$$

where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minute.

Potentially clinically significant values (PCSV) ranges are to be applied to the ECG parameter values as applicable (see Appendix 11.2 for PCSV definitions).

4.5.10. Physical Examination (PE) Variables

No PE variables are defined, as, if clinically significant PE abnormalities are observed, an AE is entered. Otherwise no PE examination information is collected.

4.5.11. Neurological Examination Variables

A full or brief neurological examination is to be performed at the time points indicated in Table 3. Neurological evaluations of specific domains as listed in the protocol are to be described as normal or abnormal not clinically significant or abnormal clinically significant.

Neurological findings at baseline that are not exclusionary should be recorded in the medical history. Findings at subsequent visits are to be assessed by the investigator to determine if these should be recorded as an AE. Clinically significant neurological abnormalities are recorded and will be summarized.

4.5.12. Other Safety Variables

- Joint Pain Questionnaire: A joint pain questionnaire is to be completed by the patient at the time points indicated in the Schedule of Events in Table 3. For each knee, hip, and shoulder joint, the patient is prompted to indicate if he or she has experienced worse pain. Assessments include:
  - Patients with significantly worse joint pain in any joint at each scheduled visit
  - Patients with significantly worse joint pain by joint at each scheduled visit
- Joint replacement: an end-of-study phone call was to be conducted at approximately 52 weeks after the first dose of study drug. The purpose of the end-of-study phone call was 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 were to 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. Assessments included:
  - Patients with joint replacement (all joint replacements)
  - Reason for joint replacement (all joint replacements)
  - Time to joint replacement (all joint replacements)
- Knee society score for joint replacement: an investigator-completed questionnaire that is used to objectively measure a patient's ability to function before and after total knee arthroplasty

As the study will now end when the last patient completes the week 36 visit, the week 52 phone call will not be performed for most of the patients; all available Joint Replacement information will be summarized in a listing.

4.6. Imaging

Radiographs of patients' knees, hips, and shoulders are to be taken using a standard approach at the time points indicated in Appendix 11.1, Table 3 In addition to scheduled imaging, radiographs should be considered for worsening joint pain. The investigator is to consult the sponsor prior to scheduling additional imaging. Magnetic resonance imaging of the index knee is to be performed at the time points indicated in Appendix 11.1, Table 3. In addition to scheduled MRIs, an MRI should be considered for worsening joint pain 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 4.

As described in the Charter for Arthropathy Adjudication Committee, the screening and on-study radiographs of the knees and hips are to be evaluated for joint space width to identify excessive loss of joint space. In addition, all radiographs and MRI scans are to be evaluated for the presence of adjudicated arthropathy. See Appendix 11.1, Table 3, Arthropathy Adjudication, for details on adjudication criteria.

The imaging data summaries and listings will include:

- Adjudicated accelerated arthropathy (AA):
  - Patients and events of AA
  - Subtypes of AA
  - Patients and events of destructive arthropathy (DA)
  - Time to AA
  - Time to DA
- Clinically Significant Imaging Events not Considered Arthropathies
- Adjudicated Arthropathy Findings at Event-Driven Imaging Timepoint
- Adjudicated Arthropathy Imaging Events at EOT (Week12) or EOF (Week 36) Imaging Timepoint
- Joint replacements:
  - Patients with joint replacement
  - Time to joint replacement

4.7. Pharmacokinetic Variables

The Pharmacokinetic (PK) variables are concentrations of functional REGN5069 in serum and time.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and timepoint/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 11.1. Samples positive in the REGN5069 ADA assay will be further characterized for ADA titers.

4.9. 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 are to perform the Moticon-related procedures at the time points according to Table 3. This sub-study is to 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.

The principal 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 is to also examine correlations of these gait parameters with the WOMAC pain subscale score.

Moticon sub-study will be analyzed outside of this SAP. This data will be as an Appendix of the clinical study report. All listings outputs produced under this SAP, however, will contain a MOTICON participation flag.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation (SD), minimum, maximum, and the first and third quartiles (Q1 and Q3).

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

Unless otherwise specified, table content is to be presented sorted by descending order of frequency of system organ class for the REGN5069 1000 mg group.

Study Observation Period – Unless otherwise stated, analysis of all safety and non-safety variables captured at multiple visits are to be analyzed by the following observations periods:

- *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 days from first dose of study drug to the day of last dose + 28 days (4 weeks). Summaries for the Treatment Period are based on the SAF.
- *The Follow-Up Period* is defined from the end of the Treatment Period to the Week 36 Visit/Early Termination Visit, regardless of the patient having completed the treatment period (week 12 visit) or not.
- *The Post-Follow-Up Period* is defined from the end of the Follow-Up Period to the phone call/Early Termination Visit.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics are to be descriptively summarized by treatment group, combined REGN5069, and overall based on the FAS. Parameters to be summarized include those described in Section 4.1.

5.2. Medical History

Medical history is to be descriptively summarized by treatment group, combined REGN5069 and overall for the FAS. Summaries are to show patient counts (percentages) by primary SOC and PT. The tables are to be sorted by descending order of frequency of system organ class for the REGN5069 1000 mg group. Within each primary SOC, PTs are to be sorted by descending order of frequency of system organ class for the REGN5069 1000 mg group.

5.3. Prior / Concomitant Medications

The analysis population is based on the SAF.

Prior Medications

All prior medications, dictionary coded by WHO, are to be descriptively summarized by treatment group, and combined REGN5069 based on the FAS. Summaries are to present patient counts (and percentages) for all prior medications, by descending order of frequency of ATC followed by ATC level 2, ATC level 4 and preferred term for the REGN5069 1000 mg group. In case of equal frequency across anatomic or therapeutic categories, alphabetical order is to be

used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication but may be counted several times for the same medication.

Concomitant Medications

All concomitant medications, dictionary coded by WHO, are to be descriptively summarized by treatment group, and combined REGN5069 based on the SAF. Summaries are to present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications, by descending order of frequency of ATC level 2, followed by ATC level 4 and preferred term. In case of equal frequency across anatomic or therapeutic categories, alphabetical order is to be used. Patients are to be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication.

When medication start/end date is missing, the rules for determining whether a medication is prior, concomitant, or post-treatment, are specified in Section 6.3.

Rescue Medication

The number (percentage) of patients using rescue medication during the Treatment Period are to be summarized by treatment group and overall based on the SAF. Analogous analyses are to be performed for the Follow-up Period, up to Week 24 visit. Rescue medication inadvertently collected in the diary past Week 24 (e.g. due to missing visits because of COVID-19 pandemic) will be censored and not included in the outputs.

For patients taking rescue medication, usage of rescue medications (measured in mg) is summarized by study week.

Descriptive statistics of the weekly average usage of rescue medications are to be presented by treatment group based on the SAF.

5.4. Prohibited Medications

The analysis population is based on the SAF.

The number (percentage) of patients with prohibited medications are to be descriptively summarized by treatment group, and combined REGN5069 based on the SAF. The tables are to be sorted by decreasing frequency of ATC Level 2, ATC Level 4, and preferred term in the REGN5069 1000 mg group.

5.5. Patient Disposition

The analysis population is based on the FAS.

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).

Dose modification for an individual patient is not allowed.

Patients who permanently discontinue from study drug and who do not withdraw from the study are 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 are asked to complete study assessments as follows:

- Patients who are withdrawn from the study before the primary endpoint visit (week 12) are asked to return to the clinic for 2 visits: once for an early termination visit consisting of the early termination assessments described in Table 3 and again at the primary endpoint visit (week 12).
- Patients who are withdrawn from the study after the primary endpoint visit are asked to return to the clinic for early termination assessments, only.

The disposition of patients in the study are to be summarized by treatment group, combined REGN5069 and overall for FAS.

Percentages are to be calculated using the number of screened patients as the denominator for:

- Screened patients (defined as having signed the ICF).
- Screen Fail patients. Reason for screen failure is to be provided.
- Patients treated but not randomized (if applicable)
- Patients randomized (defined as having received a randomization number per IWRS). This row is to reflect grouping based on randomization assignment.
- Patients did not meet inclusion/exclusion criteria but randomized (if applicable).

Percentages are to be calculated using the number of randomized patients as the denominator for:

- Patients randomized but not treated. This row is to reflect grouping based on randomization assignment.
- Patients randomized and treated.
- Patients treated differently than randomized. This row is to reflect grouping based on randomization assignment.
- Patients who completed study treatment, patients who discontinued treatment
- Patients who completed study treatment period (defined as completing Week 12 visit), patients who discontinued study treatment period and reason for study treatment period discontinuation, patients who had infusion interruptions and reason.
- Patients who completed study follow-up period (defined as completing Week 36 visit).
- Patients who completed the study (defined as having completed Week 52 phone call), patients who withdrew from the study and reason for study withdrawal.

In addition, a summary of the impact of COVID-19, with all information described in Section 9, will be provided.

Summary of the number (percentage) of patients in each analysis set are to be by treatment group, combined REGN5069, and overall.

Additionally, the following listings are to be provided (if applicable):

- Listing of patients treated but not randomized, patients randomized but not treated, patients randomized but not treated with the randomized treatment, patient disposition for all randomized patients, and patients prematurely discontinued from treatment, with reasons.
- Listing of screening failures and reasons for all screen-failed patients.

5.6. Extent of Study Treatment Exposure and Compliance

The analysis population is based on the SAF.

5.6.1. Exposure to Investigational Product

The treatment exposure to REGN5069 and placebo doses is calculated as:

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

The duration of exposure are to be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (percentage) of patients with exposure duration periods are to be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 4 weeks, ≥ 8 weeks.

The length of the study observation period (days) are to be calculated as:

- (Date of last study Visit [up to End of Follow-up Clinic Visit] – date of first study drug dose) +1.

The length of the total study participation period (days) will be calculated as:

- (Date of last study Visit or last Phone call - date of first study drug dose) +1

The study observation duration is to be summarized for each treatment group using the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The number (percentage) of patients with observation periods is to be presented by specific time periods. The time periods of interest are specified as: ≥ 1 day, ≥ 29 days, ≥ 57 days, ≥ 85 days, ≥ 113 days, ≥ 141 days, ≥ 169 days, ≥ 197 days, ≥ 225 days, ≥ 253 days, ≥ 365 days

5.6.2. Measurement of Compliance

Compliance with protocol-defined investigational product is to be calculated by treatment group and combined REGN5069 as follows:

- (Number of actual infusions of study drug during the exposure period) / (Number of planned infusions of study drug during the exposure period on or before the time that the patient discontinues from the treatment phase of the study) x 100%

Treatment compliance is to be presented by descriptive statistics as well as the number (percentage) of patients who have 1, 2, 3 infusions.

5.6.3. Protocol Deviations

All important and minor protocol deviations have been collected and reviewed on an ongoing basis throughout the study as described in the protocol deviation plan.

Protocol deviations are to be summarized for patients incurring any important deviation by count and percentage, and patients incurring each type of important deviation by count and percentage for FAS.

A patient listing of all important and minor protocol deviations is to be provided.

5.7. Statistical Methods for Efficacy

Unless stated otherwise, all efficacy analyses are to be based on the FAS. Confidence intervals are to be constructed with level of confidence equal to 95%. With the exception of analyses based on the PPS, models including stratifying variables are to utilize the value of these variables as captured in the IWRS system. Analyses based on the PPS are to utilize the value of these variables as captured in the EDC system.

If no more than 10% of patients are available in a stratification cell, that stratification factor will not be used.

5.7.1. Primary Efficacy Analysis

The primary efficacy endpoint is change from baseline to week 12 in the WOMAC pain subscale score.

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 are to be tested for each dose. Multiplicity adjustment for the 6 null hypotheses are to 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 is to stop and no further hypothesis in the order are to be tested.

The primary estimand for the primary objective is the difference in means between 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 are to be included in the analysis regardless of whether prohibited medication was taken.

The above primary and secondary efficacy variables are to be analyzed using a multiple imputation approach with a mixed-effect model for repeated measures (MMRM) based on the FAS.

Intermittently missing WOMAC subscale scores prior to treatment discontinuation are first to be imputed using the Markov Chain Monte Carlo method, and then the remaining missing data with a monotone missing pattern are to be imputed with a regression method. For patients who discontinued treatment due to reasons other than lack of efficacy, death or AEs, (reasons including discontinuation because of public health measures implemented in response to COVID-19, see Section 9 for details on the CRF implemented for collecting this information), their missing WOMAC subscale scores after discontinuation will be imputed under the missing-at-random assumption using the regression method with adjustment for covariates including treatment group, randomization strata (K-L category [2 to 3, or 4]), and baseline WOMAC subscale score. For patients who permanently discontinue treatment due to lack of efficacy, death or AEs, each imputed value obtained through the above method 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.

Missing data up to week 12 will be imputed 50 times to generate 50 complete data sets by using the SAS procedure PROC MI following the steps below:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 1849. Any score imputed outside the range of the WOMAC subscale score of 0-10 is to be truncated to the nearest permissible value on the WOMAC scale according to the following algorithm:
  - If the imputed score > 10, then the final imputed score will be 10.
  - If the imputed score < 0, then the final imputed score will be 0.
- Step 2: The missing data at visits subsequent to treatment discontinuation are to be imputed using the regression method for the monotone pattern with seed number 1849 and adjustment for covariates including treatment groups, randomization strata (K-L category of index knee at screening, 2-3 or 4), WOMAC score at baseline and all values at preceding visits. Scores that are imputed outside the range of the WOMAC subscale will be truncated in the same manner as in step 1. As the regression method imputes missing data sequentially by visits, the truncation will be implemented after each visit iteration, during the MI procedure.

- Step 3: For patients who permanently discontinued study treatment due to lack of efficacy, death or AEs, the initially missing and now imputed WOMAC subscale scores at visits subsequent to treatment discontinuation are to be adjusted to be centered at the mean baseline value for that treatment group, i.e.:

imputed score = initial imputed score under MAR – (mean change from baseline subscale score at the post-baseline time point for the treatment group based on patients on treatment with non-missing data at that time point).

Scores that are adjusted to outside the range of the WOMAC subscale will be truncated following the same algorithm as in step 1.

Each imputed data set is to be analyzed using a MMRM with terms for baseline WOMAC Pain subscale score, randomization strata (K-L category [2 to 3, or 4]), treatment, visit, and treatment-by-visit interaction as fixed effects. The MMRM is to be fitted using the MIXED procedure in Statistical Analysis System (SAS) with an unstructured covariance matrix to model the within-patient errors. The denominator degrees of freedom is to be estimated using Kenward-Roger's approximation. In the event a model cannot be fit due to the estimation algorithm failing to converge, the covariance matrix for within-patient errors is to be modeled by an autoregressive 1 structure, followed by a compound symmetry structure if convergence is still not achieved for the prior.

The results from the 50 analyses are combined using Rubin's formulae (PROC MIANALYZE). The least squares means estimates for the mean change from baseline to week 12, as well as the difference of the estimates between REGN5069 each dose and placebo, with the corresponding standard error, p-value and associated 95% confidence interval are to be provided. Similar estimates at other visits are also to be presented.

The hypothesis for H_1 is to be rejected when the p-value corresponding to the difference in change from baseline to week 12 between 1000 mg REGN5069 and placebo groups is less than 0.05 in WOMAC pain subscale score.

5.7.1.1. Supportive Analysis

The following two supportive primary endpoint analyses will be performed:

- WOMAC pain subscale scores averaged across Weeks 4, 8, and 12.
- WOMAC pain subscale scores averaged across Weeks 8 and 12.

The same method as for the primary endpoint will be used for handling missing data

Similarly, all supportive analyses described in Section 4.4.2.1 will be analyzed in a similar manner as the primary endpoint.

5.7.1.2. Subgroup Analysis

Descriptive analyses are to be performed on the primary endpoint and secondary endpoints of physical function subscale score and PGA to summarize the treatment effects across subpopulations defined by:

- K-L category [2-3, or 4]
- Geographical region [USA, MGU (Republic of Moldova, Georgia, Ukraine), Poland]
- Age group [< 65, >= 65]
- Sex [Male, Female]
- Weight group [< median baseline weight, ≥ median baseline weight kg]
- BMI group [≤ median baseline BMI, > median baseline BMI]
- Duration of OA (DOA) at baseline [≤ median baseline DOA, > median baseline DOA]

Forest plots for the subgroup analysis are to be provided for all above subgroups for the primary endpoint. Summaries and plots by visit are to be provided for the primary endpoint and secondary endpoints of physical function subscale score and PGA by K-L category and geographic region.

5.7.2. Analysis of Secondary and Exploratory Efficacy Variables

Analyses of continuous variables in secondary (Section 4.4.2) and exploratory (Section 4.4.3) endpoints are to use the same analysis method as the primary efficacy variables.

Analysis of categorical variables in secondary endpoints (Section 4.4.2) is to use the Cochran-Mantel-Haenszel approach stratified by the K-L category (2-3 vs 4 for index knee at screening) with missing data considered as non-response.

Exploratory endpoints for MOTICON (Section 4.9) will be addressed in a separate SAP.

Plots of mean values and change from baseline in PGA, WOMAC subscale and total score by Visit: Least Squares Mean (+/- SE) will be presented.

Cumulative distribution of percent change from baseline to Week 12 in the WOMAC pain and physical function scores will be presented by treatment group. The cumulative distribution plot displays a continuous plot of the percent change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis.

5.7.3. Adjustment for Multiple Comparison

Control for multiplicity for both the primary and key secondary efficacy analyses is described in Section 5.7.1.

5.8. Analysis of Safety Data

The analysis of safety and tolerability is to be performed on the SAF, as defined in Section 3.2.

The safety analysis is to be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, 12-lead ECG, Physical Examination, etc.) and is to be summarized by treatment group.

Treatment-Emergent Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 11.2.

The summary of safety results will be presented for each treatment group and by visit where applicable.

Study observation period: The observation period is divided into the four segments defined in Section 5.

5.8.1. Adverse Events

The verbatim text, the preferred term, and the primary SOC are to be listed in patient listings. Summaries that include frequencies and proportions of patients reporting AEs are to include the preferred terms and the SOCs.

Pre-treatment AEs are defined as AEs that developed or worsened during the Pre-Treatment Period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the Treatment Periods.

Follow-Up AEs are defined as AEs that developed or worsened after treatment period end (more than 4 weeks after the last dose of study drug) but before Week 36 visit.

The focus of adverse event reporting in the clinical study report is on TEAEs.

Summaries of TEAEs by treatment group, summarizing number (percentage) of patients within the specified category, during the study and by study period as applicable include:

- Overview of TEAEs, summarizing number of events,
  - Total number of TEAEs
  - Total number of Serious TEAEs
  - Patients with any TEAEs
  - Patients with any Serious TEAEs
  - Patients with any TEAEs leading to death
  - Patients with any TEAEs leading to withdrawal from study
  - Patients with any TEAEs leading to permanent study treatment discontinuation
- All TEAEs by SOC and PT
- All TEAEs by SOC, PT, severity

- All TEAEs by SOC, PT, relationship
- Study drug related TEAEs by SOC and PT
- TEAEs resulting in permanent study drug discontinuation by SOC and PT
- TEAEs leading to study drug infusion interruption by SOC and PT
- Serious TEAEs by SOC and PT
- All AEs by SOC and PT
- All AEs by severity
- All SAEs, by study period
- All SAEs by severity and study period
- All SAEs by relationship, treatment and follow-up period

Follow-up AEs will be summarized similarly as TEAEs, as well as AEs occurring during Treatment and Follow-up Periods combined.

Listing to include:

- Listing of AEs leading to death
- Listing of TEAEs leading to permanent study treatment discontinuation
- Listing of TEAEs leading to infusion interruption
- Listing of TEAEs leading to withdrawal from study
- Listing of patients with Serious TEAEs
- Listing of all joint replacements

Counts are to be provided according to treatment group and combined REGN5069 group for each PT within each primary SOC. Percentages are to be calculated based on the SAF in each treatment group and sorted by descending order of frequency of system organ class for the REGN5069 1000 mg group.

Within each primary SOC, PTs are to be sorted by decreasing frequency in the REGN5069 1000 mg group. For tables presenting severity of events, the worst severity is to be chosen for patients with multiple instances of the same event.

Counts of each PT in decreasing order of frequency are to also be provided. TEAEs with preferred terms ≥5% in any treatment group are to be summarized in the report.

5.8.2. Clinical Laboratory Measurements

Laboratory test results are to be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics based on the SAF by treatment group and combined REGN5069 group for Treatment Period and Follow-Up Period.

Listings are to be provided with flags indicating the out of laboratory range values.

A Treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value that was normal at Screening and Baseline but became abnormal and met PCSV criteria after treatment with study drug. Definition of PCSV is listed in Appendix 11.2. Treatment-emergent Potentially clinically significant values (PCSVs) are to be summarized based on the SAF by treatment group and combined REGN5069 group, as well as presented in a listing.

For Alkaline phosphatase, hemoglobin, WBC, ALT, AST, creatinine, potassium, bilirubin, plots of means of the observed values by visit are to be presented by treatment group. For all analytes, plots of change from baseline by visit are to be presented by treatment group.

For hs-CRP, plots of medians of the observed values and change from baseline over time are to be presented by treatment group.

If it is decided that CTX-1, P1NP, Osteocalcin, C1M, and C3M are to be measured and analyzed, the analyses will be made under a separate SAP.

5.8.3. Analysis of Vital Signs

Vital signs - temperature, blood pressure, heart rate (semi-recumbent and standing), orthostatic blood pressure/heart rate, and respiration rate- are to be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics by treatment group and combined REGN5069 for the SAF, for treatment period and follow-up period.

PCSV summary including orthostatic hypotension is to be constructed for treatment period, period and overall during the study, as well as presented in a listing.

5.8.4. Analysis of 12-Lead ECG

ECG parameters (Ventricular Rate, PR/PQ, QRS, QT and QTcF intervals) are to be summarized by baseline and change from baseline to each scheduled and collected assessment time. PCSV summary of ECG parameters is to be provided for treatment period, Follow-up period, and overall, for the SAF.

ECG status (ie, normal, abnormal) is to be reported. Shift tables are to be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment. Listings are to be provided with flags indicating the abnormal values.

5.8.5. Physical Exams

N/A

5.8.6. Joint Pain Questionnaire

The number (percentage) of patients with worse joint pain are to be summarized by visit and joint (index, non-index) based on the SAF, as well as presented in a listing.

5.8.7. Neurological Exam

New-onset clinically significant abnormal neurological examinations and the number (percentage) of patients with new-onset clinically significant abnormal neurological examinations are to be summarized by visit based on the SAF. Listings are to be provided with flags indicating the abnormal values.

5.8.8. Imaging Data

The number (percentage) of patients with images requiring arthropathy adjudication, as well as the number (percentage) of patients with confirmed adjudicated arthropathy (by type of arthropathy), as well as joint replacements and other findings are to be summarized by treatment group. A KM analysis of time to these events will be provided if data allows. Patient listings of cases confirmed by adjudication are to also be provided, as well as of clinically significant imaging findings that did not require adjudication.

5.9. Analysis of Pharmacokinetic and Immunogenicity Data

5.9.1. Analysis of Pharmacokinetics and Drug Concentration Data

The concentrations of functional REGN5069 in serum over time will be summarized by descriptive statistics for each treatment group. Plots of individual subject concentrations of functional REGN5069 in serum will be presented by actual day (linear and log scales). Plots of mean and median concentrations of functional REGN5069 in serum will be presented by nominal day (linear and log scale).

Select PK parameters may also be calculated and summarized descriptively by treatment group. No formal statistical hypothesis testing will be performed.

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

5.9.2. Analysis of ADA Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the REGN5069 ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the REGN5069 ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the REG5069 ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the REGN5069 ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values):

  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the REGN5069 ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories and at the
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects/patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects/patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects/patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN5069 will be explored by treatment groups. Plots of REGN5069 drug concentration time profiles may be provided to examine the potential impact of ADA response status, and titer on these profiles.

5.10.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA positive patients: patients with treatment-emergent or treatment-boosted response.
- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Patients with persistent treatment-emergent ADA response
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive patients:
    - Low (titer <1,000)
    - Moderate (1,000 ≤ titer ≤ 10,000)
    - High (titer >10,000)

6. DATA CONVENTIONS

The following analysis conventions are to be used in the statistical analysis.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

6.1. Definition of Baseline for Variables

Unless otherwise specified, the baseline assessment for all measurements is the latest available valid measurement prior to randomization.

6.2. Data Handling Conventions for Efficacy Data

WOMAC scores are computed when one pain item, one stiffness item, or at most 3 physical function items are missing. The missing items are to be imputed by the mean of available items within the same subscale. The scores are to be set to missing if more items are missing.

6.2.1. Handling of Missing Efficacy Data due to COVID-19 Public Health Measures

Due to public health measures implemented to address the world-wide COVID-19 pandemic, some sites may suspend onsite study visits or patients may opt not to attend. To mitigate data loss, patients may be contacted via telephone and the results of their efficacy measures transcribed verbally and entered into the eCOA devices. For analysis purposes, this data will be treated the same as efficacy data collected in an onsite visit and will be utilized in the efficacy analyses.

A sensitivity analysis will be performed excluding data collected via telephone.

6.3. Data Handling Convention for Missing Data

Date of last dose of study treatment

The date of the last infusion is equal to the last date of administration reported on infusion administration case report form page or missing if the last administration date is unknown.

Handling of Adverse Event and Infusion Site Reaction Severity

If the severity of a TEAE is missing, it is classified as “severe” in the frequency tables by severity of TEAEs.

Handling of Adverse Event Relatedness

If the assessment of relationship of a TEAE to the study drug or study conduct is missing, it is classified as “related”.

Handling of Adverse Events or Concomitant Medications with missing or partial start date/time

If the start date of an AE or concomitant medication is incomplete or missing, it is 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. Thus, if the AE does not clearly

indicate that the AE started prior to treatment or after the TEAE period, the AE is classified as "treatment-emergent". Otherwise, the missing day or month is imputed by the first of the months or first month of the year This is for classification purposes in the frequency tables and is not to be used in the listings.

Handling of Adverse Events or Concomitant Medications with missing or partial end date/time

When only year is present, missing AE/concomitant medication end day and month will be imputed to the earlier of (study end date, 31DECYYYY).

When both month and year are present, missing AE/concomitant medication end date is imputed to the last day of the month.

There is no imputing completely missing AE/concomitant medication end dates. Events with an end date missing are assumed to be ongoing at the time of data cut off.

Handling of Adverse Events classification with missing or partial date/time of first study drug administration

When the date and time of first study drug dose is missing, the date of randomization is to be used as the start date for classification of AEs.

When the time of the first study treatment dose is missing, all AEs that occurred on the date of the first study drug dose are considered as TEAEs.

Missing/Incomplete Medical history dates

Medical history start dates are used to determine the duration of OA at baseline per eCRF data. Completely missing medical history dates are not imputed. Missing month is imputed to January and missing day is imputed to the first day of the month.

Handling of missing item data on questionnaires

See section 6.2

WOMAC

See section 6.2.

Laboratory Safety Variables below LLOQ or above ULOQ

For central laboratory data below the lower limit of quantification (LLOQ), half of the lower limit value (i.e., LLOQ/2) is used for quantitative analyses.

Missing laboratory, ECG, vital sign, physical exam, neurological exam

No imputations for missing laboratory data, ECG data, vital sign data, physical examination, or neurological examination data are made.

Handling of Potentially Clinically Significant Values/Abnormalities (PCSA/PCSVs)

If patients have a missing baseline value, they are grouped in the category "normal/missing at baseline".

For PCSAs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSA is based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA is derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory are not be summarized or considered in the computation of PCSA values.

6.4. Visit Windows

By-visit analysis (including efficacy, laboratory data, vital signs, ECG, ADA) is summarized by the nominal visit number. Assessments taken outside of protocol allowable windows are displayed according to the case report form (CRF) assessment recorded by the investigator. For assessments without a nominal visit number such as Unscheduled, EOT, and EOS assessments, a visit number is assigned based on the actual visit date using the study day analysis window based on the targeted visit study day in Table 3 Schedule of Events.

The following visit windows are to be used to map the unscheduled visits, early end of treatment visits, early study termination visits and daily electronic dairy entries, based on the study day:

Visit No.	Visit	Targeted Study Days*	Analysis Window in Study Days
1	Screening	Day -30 to Day -1	≥ -30 and ≤ -1
2	Baseline**	1	1
3	Week 1	8	[2, 11]
4	Week 2	15	[12, 22]
5	Week 4	29	[23, 43]
6	Week 8	57	[44,71]
7	Week 12	85	[72,99]
8	Week 16	113	[100,127]
9	Week 20	141	[128,155]
10	Week 24	169	[156,183]
11	Week 28	197	[184,211]
12	Week 32	225	[212,239]
13	Week 36	253	[240,309]
14	Week 52	365	≥310

*Study days are calculated from the first dose of study drug (Day 1).

**For the purpose of change-from-baseline calculations, if a patient has missing data on Day 1 (Baseline Visit), the closest available data from the screening visit window may be used, unless otherwise specified.

If multiple measurements occur within the same visit window, the following rules are to be used to determine the analysis value:

- When multiple valid measurements occur within the same visit window, the one closest to the target study day is used in the analysis.
- When multiple valid measurements occur within equal distance from the target study day, the value after the target study day is used in the analysis.

Both scheduled and unscheduled measurements are considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

6.5. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables is based on available assessments of scheduled and unscheduled visits. For by visit summaries, unscheduled visits are mapped to a visit using the visit windows described in Section 6.4 and then included in the by-visit summaries. If the mapped window belongs to a visit that does not perform that assessment, the visit will be mapped to the closest visit that does perform the assessment, within the same study-period.

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

6.6. Pooling of Centers for Statistical Analyses

Pooling of centers is not planned at this time.

6.7. Statistical Technical Issues

Not applicable.

7. INTERIM ANALYSES

No interim analysis is planned for the study.

The unblinded primary efficacy analysis will be conducted when all randomized patients have been followed for 12 weeks after the first dose of study medication. The unblinded summarized results based on 12-week data is to be disclosed to the study team. No individual treatment assignments will be unblinded to personnel directly involved with the conduct of the study until after the final database lock.

8. SOFTWARE

All clinical data analyses are to be done using SAS Version 9.4 and above.

9. SUMMARY OF MEASURES AND ANALYSES ADDRESSING IMPACT OF COVID-19

In light of the public health emergency related to COVID-19, in accordance with the regulatory guidance and in order to ensure the clinical study patient's safety and the continuity of clinical study conduct and oversight, the following measures are explored and implemented for this study conduct and analysis:

1. Phone contact will be used for the remote collection of safety and questionnaire efficacy data (WOMAC, PGA, Joint pain Questionnaire).
2. Use of local laboratory locations when shipping to the Central Lab is not available
3. A Regeneron-standard CRF is implemented to collect COVID-19 related information:
   - **Subject's Visit Impact due to COVID-19:**
     - Entire visit not performed
     - Partial face to face visit
     - Remote Visit (Phone, Tele-medicine/Skype etc.)
     - Hybrid Visit (Partial face to face AND Remote Visit)
     - Home Visit by site staff or home health services
   - **Reasons:**
     - Subject unable/unwilling to travel due to COVID-19
     - Subject/Guardian under quarantine due to COVID-19
     - Limited site personnel availability due to COVID-19
     - Site closure due to COVID-19
     - Other
   - **Discontinuation of treatment or study due to COVID-19**
   - **Reasons:**
     - Subject has COVID-19
     - Subject decided to stop due to COVID-19
     - Subject can no longer travel due to COVID-19
     - Physician decision due to COVID-19
     - Sponsor decision due to COVID-19
     - Other

- **Discontinuation of study due to COVID-19**
- **Reasons**:
  - Subject has COVID-19
  - Subject decided to stop due to COVID-19
  - Subject can no longer travel due to COVID-19
  - Physician decision due to COVID-19
  - Sponsor decision due to COVID-19
  - Other
- **Complete the AE form if subject tested positive or has symptoms of COVID-19**

4. An updated version of MedDRA version 23.0 is to be released on 19 April 2020 to include new COVID-19 terms. The study team is to implement this re-released version 23.0 by 4 May 2020, in line with the currently established procedure
5. A sensitivity analysis will be performed excluding data collected via telephone, using the same method as for the primary endpoint 12-weeks analysis.

Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

10. REFERENCES

ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 1 (20/03/2020)

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, Guidance for Industry, Investigators, and Institutional Review Boards, March 2020

11. APPENDIX

11.1. Schedule of Events and Visits

Table 3: Schedule of Events

	Screening Period	Treatment Period							Follow-up Period							EOS
Study Procedure/Visit	**Screening Visit 1**	**Base-line Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**EOT Visit 7**	**ET/ JR Pre-op[10]**	**Visit 8**	**PC 1**	**Visit 9**	**PC 2**	**PC 3**	**EOF Visit 10**	**ET/ JR Pre-op[10]**	**PC 4**
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)**
Screening/Baseline																
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[1]	X	X														
Randomization		X														
Efficacy Assessments[2]																
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	
Treatment Procedures																
Check diary for recording of rescue medication use[3]			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[4]		X			X	X										
Safety Assessments																
Vital signs[5]	X	X	X	X	X	X	X	X	X		X					

	Screening Period	Treatment Period							Follow-up Period							EOS
Study Procedure/Visit	**Screening Visit 1**	**Base-line Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**EOT Visit 7**	**ET/ JR Pre-op[10]**	**Visit 8**	**PC 1**	**Visit 9**	**PC 2**	**PC 3**	**EOF Visit 10**	**ET/ JR Pre-op[10]**	**PC 4**
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)**
Orthostatic vital sign assessment[5]	X	X	X	X	X	X	X	X	X		X			X	X	
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)[6]	X						X (index knee only)	X[7]						X	X[7]	
MRI[8]	X (index knee)[9]						X (index knee)	X (index knee)[7]						X (index knee)	X (index knee)[7]	
Joint pain questionnaire[2]				X	X	X	X	X	X	X	X	X	X	X	X	
Knee Society Score (for JR follow-up)[2,10]								X							X	
Adverse events	→															
JR status questionnaire																X
Laboratory Testing																
Drug and alcohol test[11]	X	X			X	X	X	X			X			X	X	
Hematology[12]	X	X			X	X	X	X	X		X			X	X	
Blood chemistry[12]	X	X			X	X	X	X	X		X			X	X	
ESR	X															
HbA1c[12]	X															

	Screening Period	Treatment Period							Follow-up Period							EOS
Study Procedure/Visit	**Screening Visit 1**	**Base-line Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**EOT Visit 7**	**ET/ JR Pre-op[10]**	**Visit 8**	**PC 1**	**Visit 9**	**PC 2**	**PC 3**	**EOF Visit 10**	**ET/ JR Pre-op[10]**	**PC 4**
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)**
Urinalysis	X	X			X	X	X	X	X		X					
Pregnancy test (for WOCBP)[13]	X (serum)	X (urine)	X (urine)	X (urine)	X (urine)	X (urine)	X (urine)	X (serum)	X (urine)		X (urine)			X (serum)	X (serum)	
FSH[14]	X															
PK, Biomarker, and Research Samples																
PK sample		X[15]	X	X	X[15]	X[15]	X	X	X		X			X	X	
ADA samples		X (pre-dose)					X	X						X	X	
hsCRP[12]		X	X	X	X	X	X	X			X			X	X	
Research serum/plasma samples[12]		X	X	X	X	X	X	X			X			X	X	
DNA[16]		X														
RNA (whole blood)		X		X			X	X								
Moticon Insole Sub-study																
Moticon sub-study informed consent	X															
Moticon insole training[17]		X														
Moticon insole recording[18]		X					X	X								

ADA: Anti-drug antibody
EOF: End of follow-up
EOS: End of study
EOT: End of treatment
ESR: Erythrocyte sedimentation rate
ET: Early termination
FSH: Follicle-stimulating hormone
HbA1c: Hemoglobin A1c (Glycated hemoglobin)
hsCRP: high sensitivity C-reactive protein
IV: Intravenous
JR: Joint replacement
MRI: Magnetic resonance imaging
PC: Phone call
PK: Pharmacokinetic
Pre-op: Pre-operative
V: Visit
Wk: Week
WOCBP: Women of childbearing potential
WOMAC: Western Ontario and McMaster Osteoarthritis Index

1. The patient received a diary in which he/she records use of study-permitted rescue medication from baseline through the week-24 study visit. The patient received training on use of the diary (can be conducted at the baseline visit or earlier at the discretion of the investigator). The patient is required to bring the diary to each study visit and it is to 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) are to 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, study site personnel checks 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 is to be returned at the week-24 visit or at the early termination visit, if applicable.
4. Study drug administration is the last procedure at each dosing visit and is to 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 are to be observed in the clinic for 1 hour after study drug administration.
5. Refer to Section 8.2.3.1 in the protocol for more instructions surrounding the vital sign assessment and to Section 8.2.3.2 in the protocol 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 is to 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 is to complete the early termination/joint replacement pre-operative visit as per Schedule of Events and the procedures outlined in the schedule of events for joint replacement surgery follow-up. 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 is to 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 are to 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 was conducted for patients in the Moticon insole device sub-study only and was held at participating clinical sites prior to recording sessions.
18. Moticon insole recording sessions is conducted for patients in the Moticon insole device sub-study only and included a 3-minute walking test.

Table 4: Schedule of Events for Follow-up Period of Patients Who Undergo Joint Replacement Surgery

	Post-Operative[1]	**Long-Term[1]**
	Follow-up Visit 1 4 weeks after joint replacement surgery	**Follow-up Visit 2** 20 weeks after joint replacement surgery
Follow-up Study Day (Visit window, days)	**Follow-up Day 29 (±7)**	**Follow-up Day 140 (±7)**
Collection of surgically resected tissue for histological and molecular analyses	X	
Treatment		
Concomitant medications and therapy	X	X
Safety		
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[2]	X	X
Radiograph of knees, hips, and shoulders (bilateral)		X

1. Any patient who has joint replacement surgery during the study up to the end of the Follow-Up period at week 36 is to 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 is collected at the week-4 visit, including placement of the prosthesis and healing of the surgical wound. The visit at 20 weeks after surgery includes 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 is to be done by completing the Knee Society Score questionnaire for knee replacements.

11.2. Reference for Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

The PCSV criteria below should be used as a reference; the actual criteria for each study should be determined and agreed to by the study team prior to database lock as part of SAP and should be based on the study population, indication, and potential effects of study treatment.

Table 5: Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

Parameter	Treatment-Emergent PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, >5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and >20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. FDA DILI Guidance July 2009.

Parameter	Treatment-Emergent PCSV	Comments
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. FDA DILI Guidance July 2009. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤ 10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	Benichou C., 1994 3 independent criteria
Uric Acid Hyperuricemia Hypouricemia	>408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	Harrison - Principles of internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	Two independent criteria

Parameter	Treatment-Emergent PCSV	Comments
Chloride		Two independent criteria
Hypochloremia	<80 mmol/L and baseline ≥ 80 mmol/L	
Hyperchloremia	>115 mmol/L and baseline ≤ 115 mmol/L	
Sodium		Two independent criteria
Hyponatremia	≤129 mmol/L and baseline > 129 mmol/L	
Hypernatremia	≥160 mmol/L and baseline <160 mmol/L	
Potassium		FDA Feb 2005.
Hypokalemia	<3 mmol/L and baseline ≥ 3 mmol/L	Two independent criteria
Hyperkalemia	≥5.5 mmol/L and baseline <5.5 mmol/L	
Glucose		
Hypoglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and < 11.1 mmol/L (unfasted); <7 mmol/L (fasted) at baseline	ADA Jan 2008.
Albumin	≤25 g/L and >25 g/L at baseline	
hs-CRP	2 ULN or > 10 mg/L (if ULN not provided)	FDA Sept. 2005

Parameter	Treatment-Emergent PCSV	Comments
Hematology		
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	Harrison - Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline forFemale ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	Two Criteria are independent

Parameter	Treatment-Emergent PCSV	Comments
RBC	Female <3 Tera/L and baseline ≥3 Tera/L ≥6 Tera/L and baseline < 6 Tera/L Male <4 Tera/L and baseline ≥4 Tera/L ≥7 Tera/L and baseline < 7 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L and >=100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Urinalysis		
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	Two independent criteria
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.

Parameter	Treatment-Emergent PCSV	Comments
Orthostatic Hypotension	Su SBP < 160 mmHg - SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg Su SBP ≥ 160 mmHg - SBP St – Su ≤ - 30 mmHg DBP St – Su ≤ - 15 mmHg and HR change: >=30 bpm from semi-recumbent to standing	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: CPMP 1997 guideline. ICH E14 2005
HR(ECG Ventricular Rate (beats/min) in the data)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR/PQ	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms & < 120 ms at baseline	
QTcF	<u>Absolute values (ms)</u> >450 ms and baseline <=450 ms >480 ms and baseline <=480 ms >500 ms and <= 500 ms at baseline	To be applied to any kind of QT correction formula.
	<u>Increase from baseline</u> Increase from baseline 30-60 ms Increase from baseline >60 ms	ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.

11.3. Arthropathy Adjudication

Table 6: Definitions of Radiologic Findings for Adjudicated Arthropathy and Joint-Related Diseases

Feature	Definition
RPOA Type 1	Rapid loss of joint space width from baseline without evidence of bone fragmentation or destruction. • Rapid loss of joint space width must be confirmed by the adjudicator to ensure it is not impacted by inconsistency in view/projection. If inconsistencies in view/projection are present, the adjudicator may request a repeat X-ray or an MRI. • If rapid loss of joint space width from baseline is observed by X-ray, an MRI must be obtained and substantial focal or diffuse loss of hyaline/articular cartilage from baseline consistent with RPOA 1 must also be observed by MRI. • If a baseline MRI has not been obtained and the confirmatory MRI suggests that view/projection may account for the changes in JSW by X ray, the adjudicator may equest a repeat X-ray. If the confirmatory MRI is not consistent with RPOA 1 or provides an alternate explanation (eg meniscal extrusion), the adjudicator may determine that RPOA 1 is not present. • If an X-ray has not been obtained and an MRI suggests RPOA Type 1, an X-ray will be requested Rapid change in joint space width from baseline is defined as: • Knee joints o If JSW is ≥ 2mm at baseline, a decrease of ≥ 2mm or 50% from baseline JSW at any time point during the study (whichever is greater) o If JSW is <2mm at baseline or where accurate JSW measurement is not possible, a change in JSW to 0 mm o Due to technical limitations of the JSW measurement and precision error, if the JSW is ≤ 0.5 mm at baseline, RPOA Type 1 cannot be determined • Hip joints o If JSW is >1.5mm at baseline, a decrease of ≥1.5mm from baseline o If JSW is <1.5mm at baseline or where accurate JSW measurement is not possible, a change in JSW to 0 mm o Due to technical limitations of the JSW measurement and precision error, if the JSW is ≤ 0.5 mm at baseline, RPOA Type 1 cannot be determined • Any joint without previous image for comparison o If a prior image of the same joint is not available for comparison, by definition, RPOA Type 1 cannot be determined.
RPOA Type 2	Abnormal bone fragmentation or destruction over a short period of time, including limited collapse of at least one articular surface and which is observed principally by MRI but may be detected by X-rays.
Primary ON	Focal circumscribed or extended region of mottled radiolucency and sclerosis (infarcted bone) which is confirmed by MRI. No evidence of subchondral collapse or bone fragmentation preceding or concurrent with the diagnosis of primary ON.
Subchondral Stress or Insufficiency Fracture (SIF)	Subchondral radiolucency, which may have a sclerotic linear component and articular surface flattening and is confirmed by MRI. Does not include significant collapse or fragmentation of an articular surface.

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