STRIDES–1

SM04690 Trial Evaluating a Randomized Injection for Determination of Efficacy and Safety

STATISTICAL ANALYSIS PLAN

SM04690-OA-10

Study Title:	A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects
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SIGNATURE PAGE AND APPROVALS

A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects

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Biosplice Therapeutics commits to satisfying the requirements of the International Council for Harmonisation Good Clinical Practice (ICH-GCP) Guidelines regarding the responsibilities of the Sponsor, the United States (US) Code of Federal Regulations (CFR) Title 21 Parts 50, 54, 56, 312, and 314, and GCP Guidelines, as applicable.

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
AR1	Autogressive-1
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
eCRF	Electronic case report form
EOS	End of study
eqNSAID	NSAID/Acetaminophen equivalent usage score
ET	Early termination
FAS	Full Analysis Set
IP	Investigational Product
KL	Kellgren-Lawrence
MAR	Missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mJSW	Medial joint space width
MMRM	Mixed-effects model for repeated measures
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PASS	Patient Acceptable Symptom State
Pain NRS	Weekly average of daily pain numeric rating scale
PPAS	Per-Protocol Analysis Set
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event

Abbreviation	Term
SAS	Safety Analysis Set
SD	Standard deviation
SI	International System of Units
SSQ2	Symptom Severity Question 2
WHODD	World Health Organization Drug Dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WOMAC Function	WOMAC physical function subscore
WOMAC Pain	WOMAC pain subscore
WPI	Widespread Pain Index

1. BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. Today, 35 million people (13% of the US population) are 65 and older, and more than half of them have radiological evidence of OA in at least one joint. By 2030, 20% of Americans (about 70 million people) will have passed their 65th birthday and will be at risk for OA (Nevitt, Felson, & Lester, 2006).

The exact cause of OA is unknown, but it is associated with aging and normal wear on a joint. OA is characterized by the destruction of the articular cartilage, subchondral bone alterations, and synovitis. Patients present with pain and stiffness in their joints, with joints becoming stiffer and more immobile over time (Dougados & Hochberg, 2011). OA is a leading cause of physical disability in the US (Lawrence, et al., 2008).

Non-pharmacological management of OA (e.g., education, exercise, weight reduction) can only slightly reduce symptoms in affected joints (Bannuru, Kent, & McAlindon, 2015) (McAlindon, et al., 2014). Pharmacological management, specifically nonsteroidal anti-inflammatory drug (NSAID) use, has limited impact on clinical outcomes (Bellamy, et al., 2015) (Lapane, et al., 2015). Moreover, any clinical effects are short-lived and the potential side effects (particularly of oral NSAIDs), including but not limited to, cardiac, renal, and gastrointestinal (GI) effects, limit long-term use. Opioids are also frequently used in the management of OA pain, but have numerous potential side effects, ranging from addiction, a major public health concern in the US, to increased risk of falls, especially in the elderly.

There is a significant unmet need for pharmacological agents with disease-modifying properties for the treatment of OA. Most current treatments are designed only to relieve pain and reduce or prevent the disability caused by bone and cartilage degeneration. Available drug therapies target the symptoms, but not the cause, of this disease and no treatment inhibits or reverses the degenerative structural changes that are responsible for its (Nevitt, Felson, & Lester, 2006). There is a need for pharmacological agents to treat OA that have disease-modifying properties, but can also provide symptom relief (decreased pain and improved function), while still being safe to use by patients with comorbid conditions or concomitant medications (Pham, et al., 2003). Such agents could also potentially delay or reduce the need for joint replacement surgery, an end-stage option which may not be suitable for OA patients in which surgical risk is deemed too high.

In order to address the need for effective pharmaceutical agents to treat OA, Biosplice has used structure-based drug design to synthesize a small molecule inhibitor of the Wnt pathway, lorecivivint (LOR; previously SM04690), as a potential OA therapeutic to be administered as a local injection in the affected joint. The Wnt pathway plays a central role in the initiation and progression of OA pathology and is crucial in normal joint metabolism (Hochberg, et al., 2012). The Wnt pathway is a major regulator of joint development and is involved in the formation of bone, cartilage, and synovium. In osteoarthritic joints, increased Wnt signaling stimulates cartilage-destroying protease production and drives local progenitor cells to become bone-forming osteoblasts instead of cartilage-forming chondrocytes, thereby contributing to

osteophyte formation and cartilage loss (Gelse, et al., 2012). Gene polymorphisms involved in Wnt signaling are associated with an increased susceptibility to OA development (Wu, et al., 2012). Established research suggests that modulation of Wnt signaling is an attractive target for the treatment of OA.

Lorecivivint inhibits the Wnt pathway through the dual inhibition of intranuclear kinases CLK2 and DYRK1A, and thereby potentially (a) reduces signs and symptoms of knee OA via an anti-inflammatory mechanism, (b) inhibits cartilage breakdown through effects on degradative enzymes, and (c) enhances formation of cartilage through effects on progenitor cells and chondrocytes residing in the joint. Thus, LOR has the potential to affect both structural and symptomatic mechanisms underlying OA. In a previous randomized controlled, 52-week Phase 2a trial, LOR demonstrated significant improvements compared with placebo in pain, function, and medial joint space width (mJSW) in subjects with moderately to severely symptomatic knee OA (Yazici, et al., 2020). In clinical studies to date, LOR has been well tolerated with a safety profile similar to that of placebo.

2. OVERVIEW

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a single dose of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objective

The objective of this study was to determine the efficacy, safety, and tolerability of the SM04690 Injectable Suspension 0.07 mg dose in the treatment of knee OA.

3.2 Study Endpoints

3.2.1 Primary Efficacy Endpoint

Change from baseline OA pain in the target knee as assessed by the weekly average of daily pain numeric rating scale (Pain NRS) at Week 12

3.2.2 Secondary Efficacy Endpoints

1. Change from baseline OA pain in the target knee as assessed by Pain NRS at Weeks 24
2. Change from baseline OA function in the target knee as assessed by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscore (WOMAC Function) at Weeks 12 and 24
3. Change from baseline OA disease activity as assessed by Patient Global Assessment at Weeks 12 and 24
4. Change from baseline in usage of NSAIDs and acetaminophen for target knee OA pain

3.2.3 Safety Endpoints

1. Adverse events (AEs), serious AEs (SAEs), vital signs, and clinical laboratory measures for the duration of the study

3.2.4 Other Endpoints

1. Change from baseline OA pain in the target knee as assessed by WOMAC pain subscore (WOMAC Pain) at Weeks 12 and 24
2. Change from baseline OA pain, function, and stiffness as a composite outcome measure as assessed by WOMAC Total score at Weeks 12 and 24

4. OVERALL STUDY DESIGN AND PLAN

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a single dose of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects at Day 1.

4.1 Selection of Study Population

The study population included ambulatory males and females between 40 and 80 years of age, inclusive, with moderately to severely symptomatic knee OA. Complete inclusion/exclusion criteria are available in the study protocol.

4.2 Method of Treatment Assignment and Randomization

Subjects were randomized 1:1 (0.07 mg active per 2 mL injection:2 mL placebo) to each treatment group using Medidata Rave Randomization and Trial Supply Management (RTSM) with a permuted block design stratified by study site. 250 blocks of size 6 were generated for a total of 1500 possible subject slots.

4.3 Treatment Blinding

This was a double-blind study. As there are visual differences between the SM04690 and placebo solution, extra blinding procedures were established at each site as follows. Study medication was provided to the investigational center, which identified unblinded personnel who were able to prepare and perform the injection of study medication. Study personnel administering or preparing study medication minimized any contact with the subject following the injection and could not perform any study assessments throughout the duration of the study. Each site was required to document a blinding plan that identified the blinded and unblinded personnel at the investigational center and described how the study blind will be maintained.

4.4 Minimization of Missing Data

4.4.1 Collection of Clinical Outcomes

Clinical outcomes data were collected using electronic diary (see Protocol Section 7.3.8 for schedule of diary data collection). Eligibility criteria for the trial included successful completion of the electronic diary in the collection of both Pain NRS and WOMAC (see Inclusion Criteria 10-16). Use of electronic diary as well as enriching for subjects compliant with electronic diary use were specific protocol strategies designed to minimize the loss of key endpoint data.

4.4.2 Rescue Medication

Subjects were allowed to remain on their stable regimen of NSAIDs/acetaminophen during this study (see Protocol Section 7.8). Subjects were also allowed to change their usage as needed for pain management, including for the rescue of knee pain. Additionally, sites were instructed to

capture the amount and frequency of rescue medication use. This rescue medication policy, in addition to quantifying rescue medication use, was designed to minimize the loss of key endpoint data and provide assessment of the rescue medication's impact on key endpoint data.

4.4.3 Prohibited Medications, Treatments, and Procedures

During the conduct of the study, certain medications, treatments, and procedures were prohibited (see Protocol Section 7.6). The overall intent of these prohibitions was to minimize any possible bias in the assessment of the clinical trial endpoints. However, the protocol did allow for the use of these prohibited therapies if and only if they were required to ensure subject safety. Investigators were instructed to notify the sponsor's Medical Monitor, who would note the prohibited therapy as a protocol deviation. These deviations were categorized as major or minor depending on the nature and timing of the interventions. Subjects were not automatically discontinued based upon prohibited therapy use, allowing for continued data collection and assessment of the impact of prohibited therapy on key endpoint data.

4.4.4 Intermittent Missing Data

Ongoing programmatic surveillance of electronic diary and visit compliance using intranet dashboards during trial conduct led to the identification of subjects that were not compliant with their electronic diary entries. Sites were notified of possible non-compliant subjects and were instructed to address any possible technical or conduct issues with these subjects prior to key endpoint data collection times. The ongoing monitoring of electronic diary compliance was a specific strategy designed to minimize the loss of key endpoint data.

5. SAMPLE SIZE DETERMINATION

A sample size of approximately 725 subjects was initially selected for this study to yield 325 evaluable subjects per treatment group assuming 10% dropout.

One thousand Monte Carlo simulations generated baseline and follow-up data from a bivariate normal distribution for each treatment group and estimated the least squares difference between treatment and placebo in an outcome's change using a baseline-adjusted analysis of covariance (ANCOVA). The proportion of statistically significant results at $\alpha = 0.05$ was estimated as the approximate power for a sample size of 325 subjects per group.

The following assumptions were made based upon observed data in the Phase 2 dose-ranging studies (SM04690-OA-02 and SM04690-OA-04):

- For Pain NRS, assuming a baseline mean (standard deviation [SD]) of 6.0 (1.5), follow-up mean (SD) of 3.0 (3.0) for SM04690 and 3.8 (3.0) for placebo (presumed treatment difference -0.8), and a baseline to follow-up correlation of 0.25, power is estimated to be 93.5%.
- For WOMAC Function, assuming a baseline mean (SD) of 60 (14), follow-up mean (SD) of 30 (29) for SM04690 and 37.5 (29) for placebo (presumed treatment difference -7.5), and a baseline to follow-up correlation of 0.25, power is estimated to be 92.0%.
- For Patient Global Assessment, assuming a baseline mean (SD) of 55 (20), follow-up mean (SD) of 35 (27) for SM04690 and 42.5 (27) for placebo (presumed treatment

difference -7.5), and a baseline to follow-up correlation of 0.25, power is estimated to be 95.3%.

Based upon a blinded evaluation of aggregate data, sample size assumptions were reassessed, and additional Monte Carlo simulations generated. A sample size of approximately 500 subjects was re-estimated for this study to yield 225 evaluable subjects per treatment group assuming 10% dropout.

- For Pain NRS, assuming a baseline mean (standard deviation [SD]) of 6.0 (1.2), follow-up mean (SD) of 3.0 (2.4) for SM04690 and 3.8 (2.4) for placebo (presumed treatment difference -0.8), and a baseline to follow-up correlation of 0.25, power is estimated to be 94.3%.
- For WOMAC Function, assuming a baseline mean (SD) of 60 (12), follow-up mean (SD) of 30 (25) for SM04690 and 37.5 (25) for placebo (presumed treatment difference -7.5), and a baseline to follow-up correlation of 0.25, power is estimated to be 89.8%.

6. ANALYSIS POPULATIONS

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and received a study injection. The FAS is used to describe the analysis set which is as complete as possible and as close as possible to the intent-to-treat ideal of including all randomized subjects. Subjects will be analyzed as randomized for the FAS.

6.2 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) includes FAS subjects who received the correct treatment, completed the study, and did not have any protocol deviations that might impact the evaluation of efficacy outcomes (see Section 8.2). Subjects will be analyzed as randomized for the PPAS.

6.3 Safety Analysis Set

The Safety Analysis Set (SAS) includes all subjects who received a study injection. Subjects will be analyzed as treated for the SAS.

6.4 Duplicate Subjects

As part of routine monitoring, a search was conducted for subjects who inappropriately participated in more than one SM04690 study or at more than one site in OA-10. When this was confirmed during study conduct, they were withdrawn from the studies. The following subjects were considered duplicate subjects and were excluded from all analysis sets:

Unique Subject Identifier	Study ID	Subject Identifier for the Study	Comment	Start/End Date of Study Participation
SM04690-OA-11-7097051	SM04690-OA-11	7097051	Randomized and injected right knee on 2020-06-19	2020-05-29 2021-07-12

	SM04690-OA-10	4355035	Randomized and injected right knee on 2021-01-05	2020-12-29 2021-07-08
	SM04690-OA-10	7245003	Randomized and injected left knee on 2021-01-27	2021-01-19 2021-07-01
SM04690-OA-11-0067127	SM04690-OA-11	0067127	Randomized and injected right knee on 2020-06-09	2020-06-02 2021-07-08
	SM04690-OA-10	5275135	Randomized and injected right knee on 2020-12-28	2020-12-21 2021-07-06
SM04690-OA-11-7167061	SM04690-OA-11	7167061	Randomized and injected left knee on 2020-04-17	2020-04-09 2021-05-14
	SM04690-OA-10	5285009	Randomized and injected left knee on 2020-09-30	2020-09-22 2021-04-12

Adverse events for the above subjects will be listed separately.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Unless otherwise specified, efficacy analyses will be performed on the FAS and PPAS; general safety analyses will be performed on the SAS. The number of evaluable subjects in any analysis set may vary by endpoint/timepoint based on missing data.

For continuous variables, the outcome measure at each visit, as well as the absolute change (outcome at visit – outcome at baseline), will be summarized within each treatment group using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Categorical variables will be summarized with counts and percentages.

Data collected from unscheduled visits will not be included in summary tables but will be included in subject-level listings as appropriate.

7.1.1 Baseline

Baseline is defined as the last value recorded for any given parameter prior to study medication injection.

7.1.2 Mixed-Effects Model for Repeated Measures

A mixed-effects model for repeated measures (MMRM) will be used to evaluate Pain NRS, WOMAC, and Patient Global Assessment outcome measures. The null hypothesis is that the mean difference in the endpoints between the two treatment groups is zero, versus the alternative hypothesis that this difference is not zero. The hypotheses can be expressed as follows:

$$H_0: (\beta_1 - \beta_0)_t = 0$$

$$H_A: (\beta_1 - \beta_0)_t \neq 0,$$

where β_0 refers to the least squares mean change from baseline in the placebo group and β_1 refers to the least squares mean change from baseline in the active treatment group, evaluated at timepoint *t*.

For Pain NRS, the model will be estimated assuming a Toeplitz variance-covariance matrix. The Toeplitz structure is a more generalized form of autogressive-1 (AR1) structure, allowing the data to inform how the correlation between within-subject observations decreases over time instead of implicitly defining a uniform decay structure (Kincaid, 2005).

For WOMAC and Patient Global Assessment, the model will be estimated assuming an unstructured variance-covariance matrix, allowing the data to fully inform the correlation between within-subject observations (Kincaid, 2005).

MMRM presumes that missing data are not caused by something observable within the conduct of the trial (i.e. missing-at-random [MAR]). It is plausible to presume a MAR mechanism as there have been no observed tolerability issues to the administration of study injection during the prior development trials. Additionally, the study injection cannot be removed after it has been administered, eliminating study drug discontinuation as a source of treatment estimate confounding.

7.1.3 Analysis of Covariance

Analysis of Covariance (ANCOVA) will be used for continuous efficacy outcome measures to test the following hypotheses:

$$H_0: (\beta_1 - \beta_0) = 0$$

$$H_A: (\beta_1 - \beta_0) \neq 0$$

In the statement above, β is the least squares estimate in the change in the continuous efficacy outcome from baseline, where β_0 is the estimate for placebo and β_1 is the estimate for the active treatment group. The models will be adjusted for baseline value of the outcome.

7.1.4 Adjustment for Multiplicity

Familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method (Dmitrienko, Tamhane, & Bretz, 2010). All hypothesis tests will be evaluated in the sequential order described in Section 9.

7.1.5 Data Handling for Patients Who Withdrew from the Study

If a subject discontinues the study, early termination assessments will be performed according to the protocol. If these assessments occur during a scheduled visit, they will be associated with that visit for the purposes of FAS analysis.

7.1.6 Imputation of Missing Data

Sensitivity analysis will be performed using multiple imputation (MI) for the primary and secondary endpoints. Missing data will be imputed based upon the observed data for each outcome under the MAR assumption following the paradigm first developed by Rubin (Shafer, 1999). The imputation will adjust for the outcome's baseline data in a regression model with data

imputed independently for each timepoint. A total of 10 imputation datasets will be created and analyzed based upon accepted convention (Shafer, 1999). Error estimates of the multiple imputation itself, as well as an overall summary of the efficacy analysis, will be averaged across the 10 imputed datasets based upon Rubin's paradigm.

Specifically, let Q denote the imputed mean of an efficacy outcome Y subject to missing data at a given timepoint, where the estimate of that mean for any i^{th} imputation would be defined as function of both observed and missing such that

$$\widehat{Q^{(i)}} = E\left(Q^{(i)} | Y_{observed}, Y_{missing}^{(i)}, Y_{Baseline}, I(Group)\right), i = 1, \dots, 10.$$

After all 10 datasets have been imputed, the overall estimate of Q is a simple average defined as

$$\bar{Q} = \frac{\sum_{i=1}^{10} \widehat{Q^{(i)}}}{10}.$$

For this analysis using 10 imputed datasets, the variance of $\bar{Q}$ is defined as

$$Var(\bar{Q}) = 1.1B + \bar{U}$$

where B is the between imputation variance and U is the within imputation variance:

$$B = \frac{1}{9}\sum_{i=1}^{10}\left(\widehat{Q^{(i)}} - \bar{Q}\right)^2;$$

$$\bar{U} = \frac{\sum_{i=1}^{10} U^{(i)}}{10}.$$

PROC MI in SAS® will be used to impute missing data assuming missingness is monotone in pattern. If a subject is missing a baseline record causing non-monotone missingness, all non-missing post-baseline records will temporarily be set to missing as well. After the 10 imputation datasets are created, the non-missing post-baseline will be merged back in, thus creating complete datasets where only the originally missing records were imputed. Imputations will be performed with a seed of 469010.

7.1.6.1 Tipping Point Analysis

The MI paradigm, as proposed by Rubin, does not require nor assume any specific assumption about the nature of the missing data. Further, imputations can be (theoretically) created under any assumption of missing mechanism. A two-way tipping point analyses will be conducted to evaluate the robustness of the analyses with MI under the MAR assumption. With the tipping point approach, several additional MI datasets are created, each departing slightly from the assumptions used in the original analysis. The intended result is to establish a certain point in which the new shifted imputations have "tipped", or overturned, the original conclusions from the original analysis (i.e. a statistically significant result is now not statistically significant). The magnitude of the shift required to tip the analysis is then evaluated for plausibility; an

implausible shift will lead to the conclusion that the MI analysis is robust to departures from MAR assumption.

The tipping point exercise will be conducted only for MI analysis(es) that is/are statistically significant under the MAR assumption. Applicable MI analyses will be reassessed by shifting the imputed values for the treatment group by intervals of ±0.5 for Pain NRS and ±5 for WOMAC and Patient Global. An implausible shift parameter would be higher in magnitude than the observed difference in mean change in the associated outcome between the treatment and placebo groups.

7.2 Interim Analysis

There is no planned interim analysis for this study.

7.3 Efficacy Assessments

7.3.1 Pain NRS

The Pain NRS is an 11-point scale [0-10] for subject self-reporting of average knee pain in the previous 24 hours, where 0 represents no pain and 10 represents extreme pain. Subjects were prompted to report average pain in both knees daily on their electronic device (between 5:00 pm and 11:59 pm) during the screening period and on the target knee only starting from Day 1 through the end of the study. An average weekly score (referred to as Pain NRS) was calculated for each subject if they had provided a response for at least 4 out of 7 days in a given week. Weeks are defined as Day -7 through Day -1 (day before treatment) for baseline, Day 1 (day of treatment) through Day 7 for Week 1, Day 8 through Day 14 for Week 2, and so on as detailed in Appendix 1. The day on which subjects completed their scheduled study visits (e.g. Week 4 Visit, Week 12 Visit, etc.) does not impact the above definition of weeks.

7.3.2 WOMAC

The WOMAC is a widely used, proprietary outcome measurement tool used by health professionals to evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical functioning of a target joint. The WOMAC Version NRS 3.1 was to be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device 5 days after their Screening Visit or up until the day before the Day 1 visit. After Day 1, WOMAC assessments were to be completed by the subject for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Week 4 (with a window of ± 3 days) and Weeks 12, 24, and 28 (with windows of ± 7 days). The devices required subjects to enter a response for each item before proceeding to the next. If an assessment was completed more than once within a window, only the first assessment will be used for analysis. All visit windows are detailed in Appendix 1.

WOMAC consists of 24 questions in three domains: physical function (17 questions), pain (5 questions) and stiffness (2 questions). The response for each question in the NRS format ranges from 0 to 10. Each domain subscore as well as a total score are calculated by adding together the numerical responses for a range of 0 to 240 total points. For analysis, WOMAC scores will be linearly transformed to a 0-100 scale, where 0 represents no difficulty and 100 represents extreme difficulty.

7.3.3 Patient Global Assessment of Disease Activity

The Patient Global Assessment is an 11-point [0-10] NRS on which the subjects rated how they felt their target knee OA was doing, considering all the ways in which their target knee OA may have affected them. The NRS was anchored by descriptors at each end ("Very Good" on the left and "Very Bad" on the right). The Patient Global Assessment was to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device 5 days after their Screening Visit or up until the day before the Day 1 visit. After Day 1, Patient Global Assessments were to be completed by the subject in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic device at Week 4 (with a window of ± 3 days) and Weeks 12, 24, and 28 (with windows of ± 7 days). If an assessment was completed more than once within a window, only the first assessment will be used for analysis. All visit windows are detailed in Appendix 1. For analysis, Patient Global Assessment scores will be scaled to 0-100, where 0 represents "Very Good" and 100 represents "Very Bad".

7.3.4 NSAID/Acetaminophen Usage

Information about NSAID and acetaminophen usage was collected as part of concomitant medications at all visits. Subjects were asked to recall the name, usual total daily dose, and usual number of days taken per week of any NSAID or acetaminophen during the previous 4 weeks. Assessment of NSAID/acetaminophen usage on Day 1 prior to study medication administration will be used to establish the subject's baseline 4-week NSAID/acetaminophen usage.

Starting at Week 4 and at all subsequent in-person and phone visits until Week 28 [End of study (EOS)] or ET, subjects were asked about their NSAID/acetaminophen usage during the previous 4 weeks. This information (name, usual total daily dose, usual number of days taken per week) was documented as concomitant medications. The Investigator then compared the data with the baseline information obtained on Day 1. If there was a change from baseline, the Investigator first assessed whether the change was clinically relevant and, if clinically relevant, whether it was due to the subject's target knee OA pain.

7.4 Safety Assessments

7.4.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IP or other protocol-imposed intervention, regardless of attribution. Signs and symptoms of exacerbation or worsening of target knee OA were captured in the context of efficacy assessments. Anticipated fluctuations or anticipated deterioration (in the opinion of the Investigator) of the underlying disease (target knee OA) were not considered as AEs.

Severity was assessed utilizing the CDISC AESEV, which classifies AEs as mild, moderate, or severe. For analysis, relationship will be dichotomized into Unrelated (combining Not Related and Unlikely Related) and Related (combining Possibly Related and Probably Related).

7.4.2 Vital Signs and Weight

Vital signs were measured by a qualified staff member at Screening Visit, Day 1, and Weeks 4, 12, 24, and 28 (EOS) or ET. At each time point, the following vital were measured:

- Body temperature

- Pulse rate
- Respiratory rate
- Blood pressure (systolic and diastolic) after the subject rests (sitting or supine) for at least 5 minutes

Any measurement that was, in the opinion of the Investigator, abnormal AND clinically significant was considered as medical history if found prior to study medication injection or as an AE if found after study medication injection.

Weight measurements will be taken at the Screening Visit and at Week 28 (EOS) or ET.

7.4.3 Clinical Laboratory Evaluations

Fasting specimens for clinical laboratory analysis were to be collected at Screening Visit and Weeks 4, 12, 24, and 28 (EOS) or ET. At a minimum, the following tests were conducted:

- ***Chemistry panel***: Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, bicarbonate, calcium (corrected total), chloride, creatinine, glucose, lactate dehydrogenase, potassium, sodium, bilirubin (total)
- ***Hematology***: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count
- ***Urinalysis:*** Clarity, specific gravity, pH, protein, glucose, ketones, nitrite, leukocyte esterase, and occult blood

Urine microscopy was to be performed if urinalysis urine protein, leukocyte esterase, occult blood, or nitrite values were out of range, or if the Investigator deemed that the microscopy was clinically warranted

8. STUDY SUBJECTS AND DEMOGRAPHICS

8.1 Disposition of Subjects and Withdrawals

Subject disposition will be presented in a summary table detailing the number and percentage of subjects who were consented, randomized, treated, completed the study, or discontinued (e.g. adverse event, subject decision, etc.) overall and by treatment group. Additionally, subject disposition for randomized subjects will be presented by treatment group and study site. Additional tables will be prepared to summarize the number of subjects enrolled under each protocol version and included in each analysis set. The disposition for individual subjects will be listed along with additional information on discontinued and screen failed subjects.

8.2 Protocol Deviations

A protocol deviation is defined as any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff.

Deviations are summarized into one of the following categories:

- Informed Consent Form
- Enrollment

- Procedures
- Labs/Specimens
- Study Visits
- Investigational Product
- Subject Non-Compliance
- Serious Adverse Events

Deviations are categorized as major or minor by a cross-functional team according to pre-defined criteria established in the Protocol Deviation Classification Guideline.

- A major deviation is defined as a divergence from the protocol that materially (a) reduces the quality or completeness of efficacy data, (b) makes the informed consent inaccurate, or (c) impacts a subject's safety, rights or welfare.
- A minor deviation is defined as a divergence from the protocol that deviates from the procedures and guidelines outlined in the protocol, but is not classified as a major deviation (i.e. the deviation does not materially (a) reduce the quality or completeness of the data, (b) make the informed consent inaccurate, or (c) impact a subject's safety, rights or welfare).

Protocol deviations may result in subject exclusion from the PPAS. Prior to unblinding, all protocol deviations were reviewed by blinded study team members to determine if the deviation could reasonably affect/confound interpretation of key efficacy endpoints and should result in the subject being excluded from the PPAS. 26 subjects with the following types of deviations were excluded from PPAS:

- Major EN01 deviations (subject randomized or enrolled without meeting eligibility criteria) related to the following:
    - Pain NRS, WOMAC Pain, or WOMAC Function: n = 4
    - Medications that may impact pain assessment at baseline: n = 5
    - Significant malalignment of anatomical axis of the target knee by radiograph: n = 7
- Major NC04 deviations (prohibited concomitant medication taken) that would affect efficacy analysis at Weeks 12 or 24: n = 9
- Major SV01 deviations (Study visit out of window) where an out of window Screening Visit impacts baseline WOMAC Pain or WOMAC Function: n = 1

A final list of protocol deviations resulting in subject or data exclusion from the PPAS can be found in Appendix 2.

Major protocol deviations will be summarized by site and category, and all protocol deviations will be listed for each subject. Additionally, the COVID-19 pandemic related protocol deviations will be summarized separately.

If the radiograph prior to study entry was rated unacceptable by central imaging vendors and repeat radiographs were also rated unacceptable, the first radiograph will serve as the baseline assessment.

8.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including sex, race, ethnicity, age at baseline (both continuous and by categorical summary), weight, height, body mass index (BMI), Kellgren-Lawrence (KL) grade, Widespread Pain Index (WPI), Symptom Severity Question 2 (SSQ2), and investigator-assessed OA laterality will be presented overall and by treatment group. Continuous variables will be summarized with descriptive statistics and categorical variables will be summarized with frequencies and percentages. The summaries will be provided for each analysis set. Subject level listings will also be provided.

8.4 Medical History

A summary of reported medical history will be provided by MedDRA system organ class on the Safety Analysis Set for each treatment group. A subject-level listing will provide further information on each event.

9. EFFICACY ANALYSIS

The statistical hypotheses being tested in this study are:

1. The least squares estimate of improvement from baseline in Pain NRS at Week 12 is greater for subjects who received SM04690 compared to placebo.
2. The least squares estimate of improvement from baseline in WOMAC Function at Week 12 is greater for subjects who received SM04690 compared to placebo.
3. The least squares estimate of improvement from baseline in Pain NRS at Week 24 is greater for subjects who received SM04690 compared to placebo.
4. The least squares estimate of improvement from baseline in WOMAC Function at Week 24 is greater for subjects who received SM04690 compared to placebo.
5. The least squares estimate of improvement from baseline in Patient Global Assessment at Week 12 is greater for subjects who received SM04690 compared to placebo.
6. The least squares estimate of improvement from baseline in Patient Global Assessment at Week 24 is greater for subjects who received SM04690 compared to placebo.

The familywise error rate will be controlled in the strong sense using the closed, fixed sequence testing method (Dmitrienko, Tamhane, & Bretz, 2010). All hypothesis tests will be evaluated in the sequential order as listed above. Although formal hypothesis testing will stop once the first non-significant result is achieved (i.e. $p > 0.05$), all subsequent results and p-values will still be reported for reference; however, no conclusion of statistical significance will be drawn from these results.

9.1 Estimands

The primary estimand for this trial is the difference between a single injection of SM04690 versus placebo in mean baseline-adjusted change in Pain NRS at Week 12, whether or not NSAIDs/acetaminophen are used (i.e. presuming a treatment policy of background NSAID and acetaminophen usage), and analyzed with MMRM, including all collected Pain NRS data in subjects in the FAS.

A summary of all estimands defined for this study is available in Appendix 3.

9.2 Primary Efficacy Analysis

9.2.1 Main Analysis

Change over time in Pain NRS will be characterized using an MMRM model to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The model will include all timepoints for subjects in the FAS and will be evaluated at Week 12.

9.2.2 Sensitivity Analysis

The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis, details of which can be found in Section 12.3. Missing data will be imputed using the MI method for additional sensitivity analysis. The main primary analysis will also be repeated for subjects in the PPAS.

9.3 Secondary Efficacy Analysis

9.3.1 Main Analysis

Change over time in secondary endpoints will be characterized using MMRM to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The model will include all timepoints for subjects in the FAS and will be evaluated for Pain NRS at Week 24 and WOMAC Function and Patient Global Assessment at Weeks 12 and 24.

9.3.2 Sensitivity Analysis

The potential confounding effect of change in NSAID/acetaminophen usage on the treatment effect will be considered for sensitivity analysis, details of which can be found in Section 12.3. Missing data will be imputed using the MI method for additional sensitivity analysis. The main secondary analyses will also be repeated for subjects in the PPAS.

9.4 Other Efficacy Analysis

Change over time in WOMAC Pain and WOMAC Total scores will be characterized using a MMRM to estimate change from baseline with treatment group, week, treatment × week interaction and baseline value as covariates. The model will include all timepoints, but will be evaluated at Weeks 12, and 24. Unadjusted 95% confidence intervals and P values will be reported.

The number and percent of subjects reporting Patient Acceptable Symptom State (PASS), 30% improvement, 50% improvement, and 70% improvement in Pain NRS, WOMAC Function, and

Patient Global Assessment will be summarized. PASS is defined as a reported value of less than or equal to 30 on a 0-100 scale. Logistic regression analysis will be implemented for improvement in these assessments as well, with 95% confidence intervals and P values reported.

The analyses described above will be performed on subjects in the FAS.

10. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety outcome measures will be performed on the Safety Analysis Set. No formal statistical tests are planned for safety.

10.1 Adverse Events

All AEs collected in this study are treatment emergent events that occur during the course of the study that are not present prior to Day 1 study medication injection, or, if present at the time of study medication injection, have worsened in severity during the course of the study. AEs will be presented in summary tables depicting the number and percent of unique subjects experiencing each AE and the number of AEs overall and within each treatment group. The following summaries will be provided:

- All AEs and all SAEs by severity and relationship to study product
- AEs by highest degree of seriousness, severity, and relationship to study drug
- AEs by MedDRA system organ class and preferred term
- AEs with incidence of greater than 2% in the active treatment group sorted by preferred term incidence
- Target-knee-related AEs and SAEs sorted by preferred term incidence
- AEs leading to study withdrawal
- SAEs in subjects diagnosed with COVID-19

Separate subject-level listings will be provided for all AEs and all SAEs.

10.2 Clinical Laboratory Evaluations

All chemistry, hematology and urinalysis results from the central laboratory will be summarized into shift tables as normal, non-clinically significant abnormal, and clinically significant abnormal. Assessments of clinical significance for abnormal values were made by the investigator on results that were outside of the normal range. Shift tables will compare the number and percent of assessments from each visit to baseline values for each treatment group.

All chemistry and hematology results from the central laboratory will be summarized for each treatment group. Descriptive statistics of each laboratory test at all timepoints will be provided along with the change from baseline at each subsequent visit. If a result is below the limit of quantification, it will be set to half the value for analysis (e.g., "< 3" will be analyzed as 1.5). The International System of Units (SI) will be used for all summaries.

Abnormal chemistry, hematology, urinalysis, and urine microscopy results for each subject will be provided in listings that will include laboratory test name, result, normal range, and an

explanation for clinically significant values. HbA1c values will be listed in conventional units (%).

10.3 Vital Signs and Weight

Weight and vital signs (including systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be summarized for each treatment group. Descriptive statistics of each parameter at baseline will be provided along with the change from baseline at each subsequent visit. A subject-level listing will also be provided.

10.4 Physical Examination

Results of the general physical and knee examinations were noted in the source documents. Any clinically significant finding noted prior to study medication injection were recorded as medical history. If it was found after study medication injection, it was reported as an AE.

11. OTHER/EXPLORATORY ANALYSIS

11.1 Sites

Randomization was stratified by site and enrollment was capped at each site. Although this should minimize site differences and potential interactions, exploratory analyses taking site into account may be conducted if anomalies in the data are observed.

12. MEDICATIONS

The summary of medications will be performed on the SAS.

12.1 Concomitant Medication

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by Anatomical Main Group (Anatomical Therapeutic Chemical, ATC, Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication by treatment group.

The subgroup of medications initiated after first exposure to study product will be summarized in the same manner. If a medication start or end date is incomplete, it will be imputed in a way that assumes maximum exposure time (see table below).

Partial Date Availability	Impute Start Date		Impute End Date	
Year (YYYY)	**Prior to Injection year**	YYYY-12-31	**Prior to end of study year**	YYYY-12-31
	Same as Injection year	Injection Date	**Same as end of study year**	End of Study Date
	After Injection year	YYYY-01-01	**After end of study year**	YYYY-01-01
Year and Month (YYYY-MM)	**Prior to Injection year and month**	YYYY-MM-[DD, last day of month]	**Prior to end of study year and month**	YYYY-MM-[DD, last day of month]
	Same as Injection year and month	Injection Date	**Same as end of study year and month**	End of Study Date
	After Injection year and month	YYYY-MM-01	**After end of study year and month**	YYYY-MM-01
Ongoing or unknown status at end of study (e.g., no end date and unknown whether ongoing)	Not Applicable		End of Study Date	
Additional Considerations	If the end date is not missing, and the imputed start date is after the end date, the start date will be set equal to the end date.		If the imputed end date is before the start date, then the imputed end date will be set equal to the start date.	

Subject-level listings containing prior and concomitant medications (WHODD coding), and procedures/non-drug therapies (MedDRA coding) will be provided and will display the dates as they were entered (not the imputed version described above).

12.2 Exposure and Compliance

All treated subjects received a single injection. A list of lot numbers used in this study will be provided in the clinical study report.

12.3 NSAID/Acetaminophen Usage

An NSAID/acetaminophen usage score (NSAID Score) will be computed as outlined in (Dougados, et al., 2011), adapted to this study design. General calculation for each applicable medication is as follows:

$$\text{NSAID Score} = \frac{[\text{eqNSAID}]\ x\ [\text{Duration of Use}]\ x\ [\text{Usual usage}]}{[\text{Time period in days}]}$$

- **eqNSAID (equivalent NSAID/Acetaminophen value)**:

$$100\ x\ \frac{[\text{Usual total daily dose}]}{[\text{Consensus dose equivalent to 150 mg Diclofenac}]}$$

The following consensus dose equivalent settings will be used:

Reference	Medication [c]	Consensus dose equivalent to 150 mg of diclofenac (in mg)
Dougados et al Table 2 [a]	Diclofenac Diclofenac sodium Cyanocobalamin;diclofenac sodium;pyridoxine hydrochloride;thiamine mononitrate	150
	Naproxen Naproxen sodium Diphenhydramine hydrochloride;**naproxen sodium** Esomeprazole magnesium;**naproxen**	1000
	Aceclofenac	200
	Celecoxib	400
	Etodolac	600
	Etoricoxib	90
	Flurbiprofen	200
	Ibuprofen Diphenhydramine hydrochloride;**ibuprofen** **Ibuprofen**;pseudoephedrine hydrochloride	2400
	Indometacin	150
	Ketoprofen	200
	Meloxicam	15
	Nimesulide	200
	Phenylbutazone	400
	Piroxicam	20
	Tenoxicam	20
Additional Medications [b]	Acetaminophen Paracetamol Butalbital;caffeine;**paracetamol** Caffeine;**paracetamol** Chlorphenamine maleate;dextromethorphan hydrobromide;**paracetamol** Chlorphenamine maleate;**paracetamol** Chlorphenamine maleate;**paracetamol**;pseudoephedrine hydrochloride Codeine phosphate;**paracetamol** Dextromethorphan hydrobromide;doxylamine succinate;ephedrine sulfate;ethanol;**paracetamol** Dextromethorphan hydrobromide;doxylamine succinate;**paracetamol** Dextromethorphan hydrobromide;guaifenesin;**paracetamol**;pseudoephedrine hydrochloride Dextromethorphan;**paracetamol**;phenylephrine Diphenhydramine hydrochloride;**paracetamol** Diphenhydramine hydrochloride;**paracetamol**;phenylephrine hydrochloride Guaifenesin;**paracetamol**;phenylephrine hydrochloride Hydrocodone bitartrate;**paracetamol** Hydrocodone;**paracetamol** Oxycodone hydrochloride;**paracetamol**	3000
	Acetylsalicylic acid;caffeine;**paracetamol**	3000
	Acetylsalicylic acid **Acetylsalicylic acid**;caffeine	3000
	Ketorolac	40
	Nabumetone	2000
	Sulindac	400

[a] This full list is taken directly from (Dougados, et al., 2011) and some medications may not have been used by any subject in this study.
[b] For medications not covered in (Dougados, et al., 2011), the above settings will be used based on decision by the Biosplice Therapeutics, Inc., medical director and some medications may not have been used by any subject in this study.
[c] Combination medications (active ingredients are semicolon separated) are analyzed after considering the amount of the active ingredient of interest (in bold)

- **Duration of Use**: This will be equal to the number of days medication was used during each 4-week period of interest: [medication end date - medication start date] + 1 (date imputations, if applicable, are performed as described in section 12.1). If medication is ongoing or end date exceeds the period of interest, the end date will be set to the maximum date of interest. If medication start date is prior to the period of interest, the start date will be set to the minimum date of interest (i.e., the maximum possible duration of use within any given time period of interest is 28 days).
- **Usual usage**:

eCRF Option	Value used in calculation
No NSAID / Acetaminophen usage	0
>0-1 days a week	0.5 / 7
2-3 days a week	2.5 / 7
4-5 days a week	4.5 / 7
6-7 days a week	6.5 / 7

- **Time period in days**: 28 days (or 4-week periods).

The sum of all medications used for each 4-week period (Total NSAID Score) will be calculated and summarized. The time periods of interest are as follows:

Nominal Time Period	Actual Study Days
Baseline	Day -28 to -1
Day 1 to Week 4	Day 1 to 28
Week 5 to Week 8	Day 29 to 56
Week 9 to Week 12	Day 57 to 84
Week 13 to Week 16	Day 85 to 112
Week 17 to Week 20	Day 113 to 140
Week 21 to Week 24	Day 141 to 168
Week 25 to Week 28	Day 169 to 196

NSAID scores are only calculated for oral medications. If a subject did not have any NSAID/acetaminophen usage during a time period, their Total NSAID score will be set to 0 for that time period. If a subject terminated from the study early, the Total NSAID score for the period in which they terminated will be considered missing (i.e., an early termination subject must be in-study for the entire 28-day period of interest to compute an NSAID score).

A statistical description (number of subjects, mean, standard deviation, median, minimum, and maximum) of Total NSAID Score at baseline will be provided along with the change from baseline at each subsequent visit. Components of the Total NSAID Score will be provided in a

listing. Investigator assessment of NSAID/acetaminophen usage will also be provided in a listing.

13. CHANGES TO PLANNED ANALYSIS

Change	Protocol Section	Rationale
Subgroup analysis in subjects having a baseline mJSW within 1.5 to 4 mm inclusive disease will not be conducted.	10.4.9	mJSW was not an inclusion criterion or an outcome measure for OA-10 and it was not assessed in all subjects

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15. APPENDICES

15.1 Appendix 1 – Visit Windows

Visit	WOMAC and Patient Global Assessment	Pain NRS
Baseline	Last value before first injection	Day -7 to -1
Week 1		Day 1 to 7
Week 2		Day 8 to 14
Week 3		Day 15 to 21
Week 4	Day 26 [a] to 32	Day 22 to 28
Week 5		Day 29 to 35
Week 6		Day 26 to 42
Week 7		Day 43 to 49
Week 8		Day 50 to 56
Week 9		Day 57 to 63
Week 10		Day 64 to 70
Week 11		Day 71 to 77
Week 12	Day 78 to 92	Day 78 to 84
Week 13		Day 85 to 91
Week 14		Day 92 to 98
Week 15		Day 99 to 105
Week 16		Day 106 to 112
Week 17		Day 113 to 119
Week 18		Day 120 to 126
Week 19		Day 127 to 133
Week 20		Day 134 to 140
Week 21		Day 141 to 147
Week 22		Day 148 to 154
Week 23		Day 155 to 161
Week 24	Day 162 to 176	Day 162 to 168
Week 25		Day 169 to 175
Week 26		Day 176 to 182
Week 27		Day 183 to 189
Week 28 (EOS)	Day 190 [a] to 204	Day 190 to 196

For the purpose of analysis, Day 1 is the date the subject was treated/injected.

[a] Subject 7445071 was the only participant in the trial that was randomized and treated on different days (randomization: 24 JUN 2020, Day -1; treatment: 25 JUN 2020, Day 1). Since the ePRO device used randomization date to set window reminders, the subject completed WOMAC and PTG for Week 4 on day 25 (instead of day 26) and WOMAC and PTG for Week 28 on day 189 (instead of day 190). The noted assessments were allowed into the intended analysis visit.

15.2 Appendix 2 – Protocol Deviations Leading to Exclusion from Per-Protocol Analysis

Subject	Deviation	Category	Details
0025086	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT IS TAKING TOPIRAMATE, AN ANTICONVULSANT, THAT FITS EXCLUSION CRITERIA #16.
0025116	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT HAS BEEN TAKING AMITRIPTYLINE HCL SINCE 2019, WHICH FITS EXCLUSION CRITERIA #15.
0135034	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT DID NOT MEET EX 4; SUBJECT HAD AN ANATOMIC TIBIOFEMORAL ANGLE (ATA) (DEG) OF 11.3.
0245067	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT WAS RANDOMIZED IN STUDY AND TREATED WITH IP DESPITE BEING INELIGIBLE AS PER INCLUSION CRITERIA 12. NON TARGET KNEE AVG PAIN NRS SCORE IS 4.5
0245086	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT DID NOT MEET WOMAC SCORE. SITE NOTIFIED SPONSOR AND REPORTED PD TO IRB
0335005	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT ENROLLED INTO STUDY, EVEN THOUGH SUBJECT DIDN'T MEET INCLUSION 4, SIGNIFICANT MALALIGNMENT OF ANATOMICAL AXIS OF THE TARGET KNEE BY RADIOGRAPH.
0335019	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT WAS RANDOMIZED DESPITE NOT MEETING INCLUSION CRITERIA #12.
0335020	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT ENROLLED INTO STUDY, EVEN THOUGH SUBJECT DIDN'T MEET INCLUSION 4, SIGNIFICANT MALALIGNMENT OF ANATOMICAL AXIS OF THE TARGET KNEE BY RADIOGRAPH.
0355022	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT WAS ENROLLED DESPITE TAKING TRAMADOL 100 MG TID ORALLY SINCE 2014.
0355039	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT'S ATA DEGREE IS 15.5 AND IS THEREFORE INELIGIBLE FOR THE STUDY, HOWEVER SUBJECT WAS RANDOMIZED.
0355069	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT TOOK PROHIBITED MEDICATION HYDROCODONE, 5 MG TABLET QD ORALLY FOR RIB FRACTURE AE FROM 14-28APR2021, STUDY DAYS 149-163.
4265140	SV01 - Study visit out of window	Study Visits	SCREENING VISIT TOOK PLACE -22 DAYS FROM DAY 1

4365104	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	PERCOCET (10-325MG) TAKEN FROM 21JAN-22JAN2021, PRN, FOR RIGHT ROTATOR CUFF REPAIR PROCEDURE. WEEK 24 VISIT WAS ON 27JAN2021.
5085106	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT TOOK 60 MG OF PREDNISONE ONCE ORALLY ON 05JAN2021 FOR TREATMENT OF INCREASED LEFT KNEE PAIN AE.
	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT TOOK 60 MG OF PREDNISONE ONCE PER DAY ON 31MAR2021 AND 01APR2021 FOR TREATMENT OF INTERMITTENT LOW BACK PAIN AE.
5185055	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT WAS RANDOMIZED WHILE TAKING 20 MG TABLET OF CYMBALTA (DULOXETINE) ORALLY QD FOR ANXIETY SINCE UN UNK 2019 AND CONMED IS STILL ONGOING.
5185100	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT RECEIVED A STEROID INJECTION IN THE NON-TARGET KNEE ON 04NOV2020 DUE TO AN INJURY.
5285008	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT'S ATA DEGREE ANGLE WAS 13.3 AT SCREENING. SUBJECT DID NOT MEET CRITERIA OF SIGNIFICANT MALALIGNMENT OF ANATOMICAL AXIS OF THE TARGET KNEE, VARUS >10 DEGREES, VALGUS >10 DEGREES, BY RADIOGRAPH
5285010	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT'S ATA DEGREE ANGLE WAS 12.9 AT SCREENING. SUBJECT DID NOT MEET CRITERIA OF SIGNIFICANT MALALIGNMENT OF ANATOMICAL AXIS OF THE TARGET KNEE, VARUS >10 DEGREES, VALGUS >10 DEGREES, BY RADIOGRAPH
5435265	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT TOOK PROHIBITED MEDICATION (PERCOCET {OXYCODONE/ACETAMINOPHEN 7.5/325}) FOR POST-OPERATIVE PAIN STARTING 26MAR2021.
5435306	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT RECEIVED A CORTICOSTEROID INJECTION ON 28JUN2021 IN THE RIGHT (NON-INDEX) KNEE DUE TO WORSENING OF OSTEOARTHRITIS.
7045202	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	PROHIBITED MEDICATION TRAMADOL (50MG), TAKEN FROM 08JAN2021 TO 12JAN2021 FOR AE.
7175060	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT DID NOT MEET EX 4; ANATOMICAL AXIS ANGLE WAS 13.4

7175084	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	SUBJECT DID NOT MEET INCLUSION 15; SUBJECT WAS PRESUMPTIVE POSITIVE FOR TCA AND PER THE LAB, NONE OF THE MEDICATIONS THEY ARE TAKING WOULD CAUSE A FALSE POSITIVE.
7285370	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT TOOK GABAPENTIN STARTED ON STUDY DAY 137 AND ONGOING THROUGH STUDY END.
7295065	NC04 - Prohibited concomitant medication taken	Subject Non-Compliance	SUBJECT RECEIVED THREE INTRA-ARTICULAR INJECTIONS IN THE TARGET KNEE OF 30MG OF ORTHOVISC CORTISONE FROM 25FEB2021 - 11MAR2021.
7445103	EN01 - Subject randomized or enrolled without meeting eligibility criteria	Enrollment	WOMAC SCORE NOT DONE.

15.3 Appendix 3 – Estimands

	Estimator	Variable	Population	Intercurrent events	Population level summary
Primary	Main	Change from baseline in Pain NRS at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Pain NRS at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in Pain NRS at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in Pain NRS at Week 12	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from baseline in Pain NRS at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Pain NRS at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in Pain NRS at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in Pain NRS at Week 24	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from baseline in WOMAC Function at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in WOMAC Function at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in WOMAC Function at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in WOMAC Function at Week 12	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from baseline in WOMAC Function at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in WOMAC Function at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in WOMAC Function at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in WOMAC Function at Week 24	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from baseline in Patient Global at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Patient Global at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in Patient Global at Week 12	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in Patient Global at Week 12	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

	Estimator	Variable	Population	Other intercurrent events	Population level summary
Secondary	Main	Change from baseline in Patient Global at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using MMRM with treatment group, week, treatment × week interaction and baseline value as covariates.
	Sensitivity 1	Change from baseline in Patient Global at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with missing data imputed using the MI method; followed by tipping point analysis.
	Sensitivity 2	Change from baseline in Patient Global at Week 24	FAS	1) Prohibited medications: treatment policy strategy; analysis will be conducted regardless of use of prohibited medications. 2) NSAID/acetaminophen: composite strategy; the use of NSAIDs/acetaminophen will be considered in the analysis by adding change from baseline in Total NSAID Score at the corresponding week as a covariate to the analysis model.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA with change in Total NSAID Score as a covariate.
	Sensitivity 3	Change from baseline in Patient Global at Week 24	PPAS	1) Prohibited medications: principal stratum strategy; subjects who used prohibited medications will be excluded from this analysis. 2) NSAID/acetaminophen: treatment policy strategy; analysis will be conducted regardless of change in NSAID/acetaminophen regimen.	Difference in the change from baseline between SM04690 and placebo using baseline-adjusted ANCOVA. By definition, the PPAS will not include subjects with missing data.

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