STATISTICAL ANALYSIS PLAN (SAP)

SM04690-OA-06 – Phase B

Study Title:	A Phase 2, 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of Two Injections of SM04690 Injected in the Target Knee Joint of Moderately to Severely Symptomatic Osteoarthritis Subjects
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SIGNATURE PAGE AND APPROVALS

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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
β-CTX	β-C-terminal telopeptide
BMD	bone mineral density
CV	coefficient of variation
COMP	cartilage oligomeric matrix protein
DXA	dual-energy x-ray absorptiometry
eCRF	electronic case report form
EOSa	Phase A End of Study
EOSb	Phase B End of Study
ET	early termination
FAS	Full Analysis Set
FASB	Full Analysis Set Phase B
MAR	missing at random
mFAS	Modified Full Analysis Set
MMRM	mixed-effects model for repeated measures
mJSW	medial joint space width
OA	osteoarthritis
Pain NRS	weekly averages of daily pain numeric rating scale
P1NP	N-terminal propeptide of procollagen type I
PPAS	Per-Protocol Analysis Set
PPASB	Per-Protocol Analysis Set Phase B
qCT	quantitative computed tomography
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SAS	Safety Analysis Set
SASB	Safety Analysis Set Phase B
SD	standard deviation
SI	International System of Units
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WOMAC Function	WOMAC physical function subscore
WOMAC Pain	WOMAC pain subscore

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, Samumed 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 concentration of SM04690 injected every 6 months into the target knee joint of moderately to severely symptomatic OA subjects. In this study, “placebo” refers to vehicle.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objective

3.1.1 Primary Objective

The primary objective of this study was to evaluate the safety and tolerability of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee osteoarthritis (OA).

3.1.2 Secondary Objectives

The secondary objectives of this study were:

1. To evaluate the effectiveness of SM04690 Injectable Suspension administered every 6 months through 52 weeks for the treatment of knee OA
2. To evaluate the use of quantitative computed tomography (qCT) to assess knee bone mineral density (BMD)
3. To evaluate the safety, tolerability, and effectiveness of SM04690 Injectable Suspension from 52 weeks through 104 weeks

3.2 Study Endpoints

3.2.1 Phase A General Safety Endpoints

1. Adverse events (AEs), serious adverse events (SAEs), vital signs, and clinical laboratory measures through Week 52

3.2.2 Phase A Bone Imaging Endpoints

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 52 compared to placebo
2. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week 52 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by dual-energy X-ray absorptiometry (DXA) at Week 24 and 52

3.2.3 Phase A Efficacy Endpoints

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain numeric rating scale (NRS) from baseline through Week 52 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily pain NRS through Week 52 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC physical function subscore (WOMAC Function) from baseline through Week 52 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 52 elapsed from prior injection to repeat injection
5. Characterization of change in medial joint space width (mJSW) as measured by radiograph of the target knee from baseline through Week 52 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 52 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC pain subscore (WOMAC Pain) from baseline through Week 52 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 52 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global Assessment from baseline through Week 52 accounting for repeated injections
10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 52 elapsed from prior injection

to repeat injection

3.2.4 Phase A Exploratory Biomarker Endpoints

1. Change from baseline in serum bone biomarkers (e.g., N-terminal propeptide of procollagen type I [P1NP] and β-C-terminal telopeptide [β-CTX]) and a serum cartilage biomarker (e.g., cartilage oligomeric matrix protein [COMP]) through Week 52 compared to placebo

3.2.5 Phase B General Safety Endpoints

1. AEs, SAEs, vital signs, and clinical laboratory measures from Week 52 through Week 104

3.2.6 Phase B Bone Imaging Endpoints

1. Actual BMD and change from baseline in BMD in the target knee as assessed by qCT through Week 104 compared to placebo
2. Within-subject difference in BMD from baseline through Week 104 between the target and non-target knee by qCT for SM04690
3. Within-subject difference in BMD from baseline through Week 104 between the target and non-target knee by qCT for placebo
4. Change from baseline in BMD in the spine and hips as assessed by DXA through Week 104

3.2.7 Phase B Efficacy Endpoints

1. Characterization of change in OA pain in the target knee as measured by the weekly averages of daily pain NRS from baseline through Week 104 accounting for repeated injections
2. Characterization of change durability of treatment response in OA pain in the target knee as measured by the weekly averages of daily pain NRS through Week 104 elapsed from prior injection to repeat injection
3. Characterization of change in OA function in the target knee as measured by WOMAC Function from baseline through Week 104 accounting for repeated injections
4. Characterization of change durability of treatment response in OA function in the target knee as measured by WOMAC Function through Week 104 elapsed from prior injection to repeat injection
5. Characterization of change in mJSW as measured by radiograph of the target knee from baseline through Week 104 accounting for repeated injections
6. Characterization of change durability of treatment response in mJSW as measured by radiograph of the target knee through Week 104 elapsed from prior injection to repeat injection
7. Characterization of change in OA pain in the target knee as measured by WOMAC Pain from baseline through Week 104 accounting for repeated injections
8. Characterization of change durability of treatment response in OA pain in the target knee as measured by WOMAC Pain through Week 104 elapsed from prior injection to repeat injection
9. Characterization of change in OA disease activity as measured by Patient Global

Assessment from baseline through Week 104 accounting for repeated injections

10. Characterization of change durability of treatment response in OA disease activity as measured by Patient Global Assessment through Week 104 elapsed from prior injection to repeat injection

3.2.8 Phase B Exploratory Biomarker Endpoints

1. Change from Week 52 in serum bone biomarkers (e.g., P1NP and β-CTX) and a serum cartilage biomarker (e.g., COMP) through Week 104

4 OVERALL STUDY DESIGN AND PLAN

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

Core Phase (Phase A)

Subjects participated in a screening period of a minimum of 10 days and up to 19 days and a 52-week evaluation period. Each subject was to receive an injection on Day 1 and Week 24 (same dose for each injection) and was to be observed for one year after first injection.

Extension Phase (Phase B)

Subjects who completed Phase A were eligible to enter the extension phase, Phase B, for an additional 52 weeks of treatment. Subjects remained on their randomized treatment (SM04690 or placebo) for the additional year. Each subject was to receive an injection at Week 52 [Phase A End of Study (EOSa)] and Week 76.

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

Approximately 100 subjects were randomized 1:1 to one of two treatment groups (0.07 mg active per 2 mL injection : 2 mL placebo) using a permuted block design via Medidata Rave Randomization and Trial Supply Management (RTSM). Fifty blocks of size 4 were generated for a total of 200 possible subject slots.

4.3 Treatment Blinding

Phase A of the study was double-blind. Study medication was provided to the investigational center, and the center identified unblinded personnel who were able to prepare and perform the injection of study medication and/or placebo. Study personnel administering or preparing study medication and reference therapy were to minimize any contact with the subject following the injection and 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.

Primary analysis of Phase A data was completed after the last subject completed Week 52 (EOSa). While the Sponsor was unblinded to study treatment after the Phase A analysis (after the last subject completed Week 52 [EOSa]), the Investigators and the subjects remained blinded for Phase B.

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 6-10). Use of electronic diary as well as enriching for subjects compliant with electronic diary use during the screening period were specific protocol strategies designed to minimize the loss of key endpoint data.

4.4.2 Prohibited Medications, Treatments, and Procedures

During the conduct of the study, several 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 there 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. 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.

4.4.3 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 ANALYSIS AND REPORTING

5.1 Phase A Analysis

Primary analysis of Phase A data was completed after the last subject completed the Week 52 (EOSa) visit. A separate SAP was prepared for Phase A analyses.

5.2 Phase B Analysis

Phase B endpoints will be analyzed in a similar fashion as Phase A endpoints. This analysis plan is only focused on Phase B analysis.

6 SAMPLE SIZE DETERMINATION

The sample size for this trial was based upon accepted investigational studies exploring changes in bone density.

Based upon the subchondral BMD data obtained using qCT in SM04690-01, a coefficient of variation (CV) of 0.30 was presumed to be shared by both treatment and placebo groups; this presumed CV is larger than the observed CVs in SM04690-01. Assuming a Type 1 error of 0.05, 100 subjects (50 subjects per group) will provide 81.6% power to estimate a BMD ratio (SM04690 : placebo) of 0.93 with a one-sided confidence interval extending to 0.80 assuming a non-inferiority design.

7 ANALYSIS POPULATIONS

7.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and received at least one 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.

7.2 Full Analysis Set Phase B

The Full Analysis Set Phase B (FASB) includes all FAS subjects who received at least one study injection in Phase B. Subjects will be analyzed as randomized for the FASB.

7.3 Modified Full Analysis Set

The modified Full Analysis Set (mFAS) includes all FAS subjects who received both scheduled Phase A injections into the target knee (Day 1, Week 24). Subjects will be analyzed as randomized for the mFAS.

7.4 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (PPAS) includes all mFAS subjects who completed Phase A of the study (i.e. subjects who terminate the study early will be excluded) and did not have any protocol deviations that may have impacted the evaluation of efficacy outcomes (see Section 9.2). Subjects will be analyzed as randomized for the PPAS. A list of subjects excluded from PPAS can be found in the Phase A SAP.

7.5 Per-Protocol Analysis Set Phase B

The Per-Protocol Analysis Set Phase B (PPASB) includes all PPAS who completed Phase B of the study and did not have any protocol deviations in Phase B that may have impacted the evaluation of efficacy outcomes (see Section 9.2). Subjects excluded from per-protocol analysis in Phase A are by definition excluded from per-protocol analysis in Phase B. Subjects will be analyzed as randomized for the PPASB.

7.6 Safety Analysis Set

The Safety Analysis Set (SAS) includes all subjects who received at least one study injection. Subjects will be analyzed as treated on Day 1 for the SAS. In this study, the FAS and SAS are identical, but for consistency with other studies, the SAS will be used in summaries of safety.

7.7 Safety Analysis Set Phase B

The Safety Analysis Set Phase B (SASB) includes all subjects who received at least one study injection in Phase B. Subjects will be analyzed as treated on Day 1 for the SASB. In this study,

the FASB and SASB are identical, but for consistency with other studies, the SASB will be used in summaries of safety.

8 GENERAL ISSUES FOR STATISTICAL ANALYSIS

8.1 General Statistical Methodology

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, standard deviation (SD), median, minimum, and maximum). The number of evaluable subjects in any analysis set may vary by endpoint/timepoint based on missing data. Categorical variables will be summarized with frequency tables.

All subject-level listings will be comprehensive and include subjects enrolled in both Phase A and Phase B. Data collected from unscheduled visits will not be included in summary tables but will be included in subject-level listings as appropriate.

8.1.1 Baseline

Baseline is defined as the last value recorded for any given parameter prior to first study medication injection on Day 1. For qCT and DXA, values recorded from Screening Visit 2 will serve as baseline, regardless of whether the scans took place before or after first study medication injection. Baseline values for Phase B of the study are the same as they were for Phase A.

8.1.2 Analysis of Covariance (ANCOVA)

ANCOVA models will be used to analyze change over time in bone imaging endpoints. All models will be adjusted for baseline. Least squares estimates, two-sided 95% confidence intervals (unadjusted for multiplicity), and effect sizes will be provided.

8.1.3 Mixed-Effects Models for Repeated Measures

A mixed-effects model for repeated measures (MMRM) will be used to analyze change over time in 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).

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.

8.1.4 Data Handling for Subjects Who Withdrew from 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 analysis.

8.1.5 Imputation of Missing Data

No imputation will be performed for Phase B efficacy analysis.

8.2 General Safety Assessments

8.2.1 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).

8.2.2 Vital Signs and Weight

Vital signs were measured by a qualified staff member at all visits except Screening Visit 2. At each time point, the following vital signs were to be 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 were to be taken at Screening Visit 1 and at Weeks 24, 52 (EOSa), 76, and 104 [Phase B End of Study (EOSb)] or ET.

8.2.3 Clinical Laboratory Evaluations

Fasting samples for clinical laboratory analysis were to be collected at Screening Visit 2 and Weeks 4, 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) 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, leukocytes, 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

8.3 Bone Imaging Assessments

8.3.1 Knee BMD (qCT)

qCT scans of both knee joints were to be taken at Screening Visit 2 and at Weeks 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) or ET. The qCT scans assessed changes in BMD in both tibias across three compartments (medial, lateral, and total [medial + lateral]) and four volumes of interest (subchondral epiphysis, mid-epiphysis, juxtaphysis, and total).

For analysis, values of BMD that have undergone longitudinal correction will be used when available. Refer to Bioclinica's *Imaging Review Charter* for details on how corrections may have been made for scanner quality control.

8.3.2 Spine and Hip BMD (DXA)

Bone density DXA scans of the spine and hips were to be taken at Screening Visit 2 and at Weeks 24, 52 (EOSa), 76, and 104 (EOSb) or ET. Spine DXA scans assessed changes in BMD in two regions of interest: total (lumbar vertebrae L1 to L4) and adjusted total (L1 to L4 excluding any vertebral levels due to artifact). Hip DXA scans assessed changes in BMD in two regions of interest: total hip and femoral neck.

The DXA scanning assessed changes in the hips and spine and included the following parameters:

- **BMD**: individual subject's test, measured in g/cm^2
- **T-score**: The number of standard deviations a subject's BMD differs from the mean BMD of a young, healthy sex-matched adult population
- **Z-score**: The number of standard deviations a subject's BMD differs from the mean BMD for an age-matched and sex-matched healthy population.

Negative T- and Z-scores indicate results below population mean, and positive scores indicate results above population mean. All T-scores were determined using reference data for Whites regardless of the individual subject's race. Z-scores were determined using African American reference data for Black or African American subjects. All other races or those with unknown race used the White reference data for Z-score calculations. Spine reference values were based on manufacturer's reference data; total hip reference values were based on NHANES-98 data.

For safety analysis, values of BMD and T-scores that have undergone longitudinal correction will be used when available. Refer to Bioclinica's *Imaging Review Charter* for details on how corrections may have been made for scanner quality control. Z-scores will not be summarized.

8.4 Efficacy Assessments

8.4.1 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 on their electronic device to report average pain daily (between 5:00 pm and 11:59 pm) in both knees at Screening Visit 2 and on the target knee only through the end of the study. An average weekly score (referred to as Pain NRS) will be 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.

8.4.2 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 questionnaire 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 5 days after Screening Visit 2 or up until the day before the Day 1 visit. After Day 1, monthly (every 4 weeks, with a window of ± 3 days) WOMAC assessments were to be completed by the subjects for their target knee in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. At Weeks 24, 52 (EOSa), and 76, the WOMAC questionnaire must have been completed prior to the study medication injection; otherwise the results were not used in analysis. 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.

8.4.3 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, considering all the ways in which their target knee OA may affect them. The NRS is anchored by descriptors at each end (“Very Good” on the left and “Very Bad” on the right). The 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 5 days after their Screening Visit 2 or up until the day before the Day 1 visit. After Day 1, monthly (every 4 weeks, with a window of ± 3 days) Patient Global Assessments were to be completed by the subjects in the evening (between 5:00 pm and 11:59 pm) remotely on their electronic devices. At Weeks 24, 52 (EOSa), and 76, the Patient Global Assessment must have been completed prior to the study

medication injection; otherwise the results were not used in analysis. 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, scores will be linearly transformed to a 0-100 scale, where 0 represents "Very Good" and 100 represents "Very Bad". If an assessment was completed more than once within a window, only the first assessment will be used for analysis.

8.4.4 mJSW

Radiographs of the knee joints were to be taken at Screening Visit 1 and at Weeks 24, 52 (EOSa), 76, and 104 (EOSb) or ET. Bilateral radiographs were to be taken in a weight-bearing fixed flexion position, using a posterior-anterior view X-ray. All radiographs were submitted to an independent radiologist at the central imaging vendor who documented disease stage according to the Kellgren-Lawrence grading scale for compliance with inclusion/exclusion criteria, as well as mJSW for efficacy assessments. mJSW measurements will be reported to two decimal places.

8.5 Exploratory Biomarker Assessments

Blood samples for biomarker analysis were to be collected at Screening Visit 2 and Weeks 4, 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) or ET. Biomarkers that were assessed included, but were not limited to, bone biomarkers (P1NP and β-CTX) and a cartilage biomarker (COMP).

9 STUDY SUBJECTS AND DEMOGRAPHICS

9.1 Disposition of Subjects and Withdrawals

Subject disposition will be presented in a summary table detailing the number and percentage of subjects who were randomized, treated in Phase B, completed Phases A and B of the study, and discontinued (e.g. subject withdrawal, adverse event, 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 Phase B analysis set. The disposition for individual subjects will be listed along with additional information on discontinued subjects.

9.2 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:

- Investigational Product
- Informed Consent
- Enrollment
- Procedures
- Labs/Specimens
- Study Visits
- Source Documentation

- Diaries, Questionnaires, or Patient Reported Outcomes
- 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 PPASB. Prior to Phase B database lock, all protocol deviations were reviewed by study team members to determine if the deviation could reasonably affect/confound interpretation of efficacy endpoints and should result in the subject being excluded from the PPASB. Subjects with the following types of deviations were excluded from the PPASB:

- Subjects taking pain medications that may significantly impact pain and function assessment

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

Major protocol deviations that occurred in Phase B 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 that occurred in Phase B will be summarized separately.

For deviations associated with a study visit, only those occurring at Week 64, Week 76, Week 88, or Week 104 (EOSb) will count as Phase B deviations. For deviations not associated with a study visit (e.g. prohibited medications), the dates listed in the CRA comments were evaluated against the date of the subject's Week 52 injection. Any deviations that occurred after the Week 52 injection will be counted as Phase B deviations. Details can be found in Appendix 3.

9.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics of subjects in Phase B, including sex, race, ethnicity, age at baseline, weight, height, body mass index, KL grade, WPI, SSQ2, and mJSW, 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 the FASB and PPASB. Subject-level listings will be provided.

9.4 Medical History

A summary of medical history by MedDRA system organ class was provided in the Phase A analysis. A subject-level listing will provide further information on each event.

10 GENERAL SAFETY ANALYSIS

Whereas Phase A analysis (defined prior to unblinding) was the primary analysis for this study, data collected during Phase B complements the primary analysis by offering insight into safety after more than one year of treatment.

10.1 Adverse Events

AEs collected in this study are 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 for both the entire study length (SAS) and for Phase B (SASB) separately:

- All AEs by seriousness, 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 and SAEs by preferred term incidence
- Target-knee-related AEs and SAEs by preferred term incidence
- SAEs in subjects diagnosed with COVID-19

Subject-level listings will be provided for all AEs and all SAEs separately.

10.2 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. A comprehensive statistical description (number of subjects, mean, standard deviation, median, minimum, and maximum) of each parameter at baseline will be provided along with the change from baseline at each subsequent visit for subjects in the SAS. A subject-level listing will be provided.

10.3 Clinical Laboratory Evaluations

All chemistry, hematology and urinalysis results from the central laboratory will be comprehensively 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. Comprehensive 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 comprehensively 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 timepoint for subjects in the SAS. 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.

11 BONE IMAGING ANALYSIS

Whereas Phase A analysis (defined prior to unblinding) was the primary analysis for this study, data collected during Phase B complements the primary analysis by offering insight into safety after more than one year of treatment. Bone imaging analysis will be performed on the SAS.

A statistical description of target knee, non-target knee, spine, and hip BMD at baseline will be provided along with absolute and percent changes from baseline at each subsequent timepoint. Statistical descriptions of knee BMD for subgroups such as KL grade, sex, and age group may be provided.

Difference between target knee and non-target knee BMD will be summarized at baseline along with absolute changes from baseline at each subsequent timepoint. Spine and Hip BMD T-scores will be summarized at baseline only for subjects enrolled in Phase B.

Baseline-adjusted ANCOVA as described in Section 8.1.2 will be used to analyze the change from baseline in BMD in the target knee and evaluated at Weeks 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb).

Baseline-adjusted ANCOVA will also be used to analyze the within-subject difference in BMD between the target and non-target knee by qCT for SM04690, within-subject difference in BMD between the target and non-target knee by qCT for placebo, and change from baseline in BMD of the spine and hips by DXA for SM04690 subjects versus placebo. The models will be evaluated at Weeks 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb) for qCT and Weeks 24, 52, 76, and 104 (EOSb) for DXA.

Knee BMD analysis will include all compartments and volumes of interest. Spine BMD analysis will include the adjusted total region of interest; hip BMD analysis will include both total hip and femoral neck regions of interest.

Subject-level listings will be provided.

12 EFFICACY ANALYSIS

A statistical description of Pain NRS at baseline will be provided along with absolute changes from baseline at each subsequent timepoint for subjects in the FASB and PPASB. Statistical descriptions of WOMAC Pain, WOMAC Function, Patient Global Assessment, and mJSW at baseline will also be provided along with absolute changes from baseline at each subsequent timepoint for subjects in the FASB only.

Changes in the target knee from baseline in Pain NRS will be characterized using MMRM for subjects in the FASB and PPASB; the models will be evaluated through Week 104 (EOSb). All models will use treatment group, week, treatment×week interaction, and baseline values as covariates. Unadjusted 95% confidence intervals and P values will be reported.

If a subject submitted data related to their non-target knee due to an electronic device error, this data will not be analyzed.

Subject-level listings will be provided.

Since Phase A analysis (defined prior to unblinding) was the primary analysis for this study, there will be no estimands provided for Phase B.

13 EXPLORATORY BIOMARKER ANALYSIS

A statistical description of biomarkers COMP, P1NP, and β-CTX at baseline will be provided along with absolute and percent changes from baseline at each subsequent timepoint for subjects in the SAS.

Baseline-adjusted ANCOVA will also be used to analyze the change from baseline in these biomarkers and evaluated at Weeks 4, 12, 24, 36, 52 (EOSa), 64, 76, 88, and 104 (EOSb). Subject level listings will be provided.

14 MEDICATIONS

The summary of medications will be performed on the SASB.

14.1 Concomitant Medications

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 Week 52 injection will be summarized in the same manner. If a medication start date is incomplete, it will be imputed with the latest possible date to increase the likelihood it is included in the table of medications initiated after first exposure. For example, medication start dates of “2019” and “2020-02” would be imputed to “2019-12-31” and “2020-02-29”, respectively.

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).

14.2 Exposure

All treated subjects were scheduled to receive two injections during Phase A of the trial and two injections during Phase B of the trial. A summary table of the number injections received will be provided. A list of lot numbers used in this study will be provided in the clinical study report.

15 CHANGES TO PLANNED ANALYSIS

For the Phase B exploratory biomarker endpoint, all changes were calculated from baseline instead of from Week 52.

16 REFERENCES

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17 APPENDICES

17.1 Appendix 1 – Visit Windows

Visit	Monthly 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 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 54 to 60	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 82 to 88	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 110 to 116	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 138 to 144	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 166 to 172*	Day 162 to 168
Week 25		Day 169 to 175
Week 26		Day 176 to 182
Week 27		Day 183 to 189
Week 28	Day 194 to 200	Day 190 to 196
Week 29		Day 197 to 203
Week 30		Day 204 to 210
Week 31		Day 211 to 217
Week 32	Day 222 to 228	Day 218 to 224
Week 33		Day 225 to 231
Week 34		Day 232 to 238
Week 35		Day 239 to 245
Week 36	Day 250 to 256	Day 246 to 252
Week 37		Day 253 to 259

Week 38		Day 260 to 266
Week 39		Day 267 to 273
Week 40	Day 278 to 284	Day 274 to 280
Week 41		Day 281 to 287
Week 42		Day 288 to 294
Week 43		Day 295 to 301
Week 44	Day 306 to 312	Day 302 to 308
Week 45		Day 309 to 315
Week 46		Day 316 to 322
Week 47		Day 323 to 329
Week 48	Day 334 to 340	Day 330 to 336
Week 49		Day 337 to 343
Week 50		Day 344 to 350
Week 51		Day 351 to 357
Week 52 (EOSa)	Day 362 to 368*	Day 358 to 364
Week 53		Day 365 to 371
Week 54		Day 372 to 378
Week 55		Day 379 to 385
Week 56	Day 390 to 396	Day 386 to 392
Week 57		Day 393 to 399
Week 58		Day 400 to 406
Week 59		Day 407 to 413
Week 60	Day 418 to 424	Day 414 to 420
Week 61		Day 421 to 427
Week 62		Day 428 to 434
Week 63		Day 435 to 441
Week 64	Day 446 to 452	Day 442 to 448
Week 65		Day 449 to 455
Week 66		Day 456 to 462
Week 67		Day 463 to 469
Week 68	Day 474 to 480	Day 470 to 476
Week 69		Day 477 to 483
Week 70		Day 484 to 490
Week 71		Day 491 to 497
Week 72	Day 502 to 508	Day 498 to 504
Week 73		Day 505 to 511
Week 74		Day 512 to 518
Week 75		Day 519 to 525
Week 76	Day 530 to 536*	Day 526 to 532
Week 77		Day 533 to 539
Week 78		Day 540 to 546
Week 79		Day 547 to 553
Week 80	Day 558 to 564	Day 554 to 560

Week 81		Day 561 to 567
Week 82		Day 568 to 574
Week 83		Day 575 to 581
Week 84	Day 586 to 592	Day 582 to 588
Week 85		Day 589 to 595
Week 86		Day 596 to 602
Week 87		Day 603 to 609
Week 88	Day 614 to 620	Day 610 to 616
Week 89		Day 617 to 623
Week 90		Day 624 to 630
Week 91		Day 631 to 637
Week 92	Day 642 to 648	Day 638 to 644
Week 93		Day 645 to 651
Week 94		Day 652 to 658
Week 95		Day 659 to 665
Week 96	Day 670 to 676	Day 666 to 672
Week 97		Day 673 to 679
Week 98		Day 680 to 686
Week 99		Day 687 to 693
Week 100	Day 698 to 704	Day 694 to 700
Week 101		Day 701 to 707
Week 102		Day 708 to 714
Week 103		Day 715 to 721
Week 104 (EOSb)	Day 726 to 732	Day 722 to 728

*Note: At Weeks 24, 52 (EOSa), and 76, the WOMAC and Patient Global Assessment must be completed prior to the Week 24, 52 (EOSa), and 76 study medication injections, respectively.

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

Subjects Excluded from PPASB			
Subject	**Deviation**	**Category**	**Details**
0356016	IP08 - Prohibited concomitant medication taken	Minor	SUBJECT RECEIVED 2 ML SYNVISC INJECTIONS IN TARGET KNEE 1X/WEEK FROM 25JUN2020 TO 09JUL2020 FOR OA KNEE PAIN.
Subjects Excluded from PPAS			
Subject	**Deviation**	**Category**	**Details**
0106017	IP08 - Prohibited concomitant medication taken	Minor	OXYCODONE WAS TAKEN FROM 20NOV2019 TO 26NOV2019, 10 MG, PRN, ORAL ROUTE.
0356001	IP08 - Prohibited concomitant medication taken	Minor	SUBJECT TOOK HYDROCODONE-ACETAMINOPHEN, 5-325MG, PRN, FROM 04MAY-26MAY2019 AS TREATEMENT FOR AE OF KIDNEY STONES
0356008	DQ03 - Subject diary, questionnaire, or patient reported outcome completion outside of protocol requirements	Minor	SUBJECT WAS COMPLETING THE QUESTIONNAIRES ON THE INCORRECT TARGET KNEE FROM 21FEB2019 - 03JUL2019 DUE TO YPRIME PROGRAMMING ERROR.
0356060	IP08 - Prohibited concomitant medication taken	Minor	SUBJECT STARTED TAKING 20 MG OF AMITRIPTYLINE QD ORALLY ON 17OCT2019 FOR IRRITABLE BOWL SYNDROME AND CONMED IS ONGOING.

4136003	DQ03 - Subject diary, questionnaire, or patient reported outcome completion outside of protocol requirements	Minor	SUBJECT QUESTIONNAIRES WERE COMPLETED FOR THE INCORRECT TARGET KNEE FOR THE PERIOD OF 21FEB TO 11JUL DUE TO YPRIME PROGRAMMING ERROR.(WEEK 4 - WEEK 24 VISITS WERE AFFECTED)
4136015 **	NC01 - Subject non-compliant with protocol	Major	SUBJECT HAD A KNEE ARTHROSCOPY IN TARGET KNEE (RIGHT) (PROHIBITED PER PROTOCOL), SUBJECT WAS ONLY HOSPITALIZED FOR 8 HOURS
4266050	IP08 - Prohibited concomitant medication taken	Major	CORTICOSTEROID INJECTION WAS ADMINISTERED INTRA-ARTICULARLY INTO TARGET KNEE ON 23SEP2019. INJECTION WAS RECEIVED ONCE WITH A DOSAGE OF 1ML

** Not excluded from PPAS entirely; however, efficacy data after this deviation will be censored, allowing for evaluation of both Phase A study injections with at least 12 weeks of follow-up.

17.3 Appendix 3 – Major Protocol Deviations and COVID-19 Protocol Deviations Not Associated with a Study Visit for Subjects in Phase B

Subject	Deviation	Category	Details	Date of Week 52 Injection	Counted as Phase B Deviation?
0356044	IP08 - Prohibited concomitant medication taken	Minor	DUE TO COVID-19 AE, SUBJECT TOOK PREDNISONE 20 MG TABLET ORAL BID FROM 28DEC2020 TO 01JAN2021	2020-05-22	Yes
4136015	NC01 - Subject non-compliant with protocol	Major	SUBJECT HAD A KNEE ARTHROSCOPY IN TARGET KNEE (RIGHT) (PROHIBITED PER PROTOCOL), SUBJECT WAS ONLY HOSPITALIZED FOR 8 HOURS [Dates from PROC: 22MAY2020]	2020-07-09	No
4266050	IP08 - Prohibited concomitant medication taken	Major	CORTICOSTEROID INJECTION WAS ADMINISTERED INTRA-ARTICULARLY INTO TARGET KNEE ON 23SEP2019. INJECTION WAS RECEIVED ONCE WITH A DOSAGE OF 1ML	2020-05-26	No

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Reason for signing: Approved	Name: Jon Britt Role: Manager, Biostatistics Date of signature: 23-Sep-2021 04:45:48 GMT+0000

Reason for signing: Approved	Name: Ismail Simsek Role: Medical Director Date of signature: 23-Sep-2021 14:37:51 GMT+0000

Reason for signing: Approved	Name: Amy Halseth Role: Executive Director, Clinical Science Date of signature: 23-Sep-2021 15:17:57 GMT+0000

Reason for signing: Approved	Name: Christopher Swearingen Role: Vice President, Clinical Outcomes and Analytics Date of signature: 23-Sep-2021 15:27:13 GMT+0000

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