A DOUBLE-BLIND, RANDOMIZED STUDY COMPARING STEROID INJECTION AND BIODRESTORE™ FOR PATIENTS WITH KNEE OSTEOARTHRITIS

Protocol Summary

Title of Study:	A Double-blind, Randomized Study Comparing Steroid Injection and BioDRestore for Patients with Knee Osteoarthritis
Study Type:	Postmarket Interventional
Primary Investigator:	Paul Siffri, MD
Primary Endpoint:	Visual Analog Pain Score (VAS), VR-12, Lysholm, SANE and Knee Injury and Osteoarthritis Outcome Score (KOOS) at the 6-week, 3-month, 6-month, and 12-month post-injection time periods between the two groups.
Secondary Endpoints:	Inflammatory markers at 6 months post-injection.
Design:	Prospective, randomized, two-arm, double-blind study
Length of Study:	12M follow-up
Sample Size:	84 subjects

Schedule of Events

	BL	TX	6WK	3M	6M	12M
Informed Consent	√	-	-	-	-	-
Inclusion/ Exclusion	√	√	-	-	-	-
Demographics/ Medical History	√	-	-	-	-	-
Randomization	-	√	-	-	-	-
Physical Exam-ROM	√	-	√	√	√	√
Patient Outcomes (VAS, KOOS, Lysholm, SANE, VR-12)	√	-	√	√	√	√
Knee aspiration	-	√	-	-	√	-
X-ray	-	-	-	-	-	√
Adverse Event Assessment	√	√	√	√	√	√

1. Background

Osteoarthritis (OA), specifically involving the knee, is one of the most common causes of human disease[1] and can lead to significant pain and functional decline[2]. A potential element of OA includes degenerative tears of the knee meniscus and/or chondropathy, both of which involve destabilization from mechanical or biological issues[3].

Cortisone injections are commonly used to temporarily relieve inflammation and pain associated with osteoarthritis. The response or effect of the injection can vary, depending on the stage of OA.[4] Advanced OA where little cartilage remains may not provide enough joint space for the injection to be effective. Cortisone injections can also potentially cause an adverse reaction in certain patient populations, particularly patients with diabetes who may experience a significant increase in blood sugar after a cortisone injection.[5]

Alternatives to cortisone injections include viscosupplementation, platelet-rich plasma (PRP) injections and stem-cell therapy. One form of therapy that has shown promising results with little reported on in literature is amniotic tissue matrices, to include BioDRestore™ Elemental Tissue Matrix. BioDRestore is a "morselized, flowable tissue allograft derived from amniotic tissues. Amniotic tissues have been shown to support soft tissue repair, reduce inflammation and minimize scar tissue formation". [6,7]

This study will compare corticosteroid injection to BioDRestore injection in patients with significant (Kellgren-Lawrence grade 3-4) knee osteoarthritis. Our hypothesis is that BioDRestore will result in better outcomes than corticosteroid when injected intra-articularly in patients with knee OA.

2. Study Endpoints

Primary Endpoint

- Visual Analog Score (VAS), VR-12, Lysholm, SANE and Knee Injury and Osteoarthritis Outcome Score (KOOS) at the 6-week, 3-month, 6-month, and 12-month post-injection time periods.

Secondary Endpoints

- Inflammatory markers at 6-months post-injection.

3. Subject Recruitment and Screening

Screening

Patients who present with osteoarthritis of the knee and are recommended for a knee injection will be screened for inclusion into the study. Following discussion of the study between the patient and the treating physician, the patient will be given the opportunity to move forward with the informed consent process.

Enrollment

The subject will be considered enrolled once voluntary informed consent has been given, and the form has been signed and dated by all required parties.

Randomization

Subjects will be randomized to a treatment arm (corticosteroid or BioDRestore injection) using a 1:1 ratio. Once study eligibility has been confirmed, the study coordinator or designee will randomize the subject to a treatment arm. The treatment for each subject will be assigned through the study database.

Blinding

Study subjects and investigators will be blinded to the treatment assignment for the duration of the study to reduce the risk of bias. The research coordinator will provide the randomization to the investigator's medical assistant (MA) prior to treatment in order for the MA to assist with preparation of the injection.

3.1. Inclusion Criteria

Subjects must meet all of the following characteristics for inclusion in the study.

- Male or female, aged 18 to 80 years.
- Willing and able to give voluntary informed consent to participate in this investigation.
- Patient presents with knee osteoarthritis and Kellgren Lawrence grade 3-4 (OA diagnosed and confirmed by treating physician using standing x-ray).
- Candidate for intra-articular knee injection.
- BMI < 40

3.2. Exclusion Criteria

Subjects with any of the following characteristics must be excluded from participation in the study:

- Patients who have received intra-articular injection(s) in the last 3 months.
- Patients who have undergone arthroscopic surgery on the study knee in the past year.
- Patients who have undergone arthroplasty on the study knee.
- Ligament instability
- Diabetes (Type 1 or II)
- Inflammatory arthropathies.
- Fibromyalgia or chronic fatigue syndrome.
- Female patient who is pregnant or nursing.
- Chronic use of narcotics.
- Any other reason (in the judgment of the investigator).

3.3. Withdrawal of Subjects from Study

Voluntary Withdrawal by Subject

Study participation is voluntary and subjects may withdraw at any point during the study. If a subject withdraws from the study, the investigator will make all reasonable efforts to determine the reason for the subject's withdrawal and will document the reason on the applicable form and in the patient's medical record. After a subject withdraws from the study, no effort will be made to replace or follow the subject. However, the subject will still be offered clinical management of their knee condition.

Withdrawal by Investigator

The investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- Occurrence of a serious adverse event
- Investigator's discretion to withdraw subject for safety reasons
- Subject noncompliance with visits and/or assessments
- Subject is lost to follow-up (as defined below)

Lost to Follow-Up

Subjects will be defined as lost to follow-up when the following procedures have been documented in the subject's source documentation:

- At least 2 phone calls made on separate dates to the subject are not returned
- A letter is sent to the subject's last known address and the subject does not reply after 30 days.

4. Informed Consent

Investigators are responsible for obtaining and documenting the voluntary informed consent of the study subjects prior to conducting any study-related assessments per 21 CFR Part 50. Prior to beginning the trial the investigator must obtain written and dated approval of the informed consent form. Subjects will receive a copy of the initial signed and dated informed consent form prior to the subjects' participation in the trial and any revised informed consent forms during the duration of the trial.

The subject must sign and date the consent form in the presence of the investigator, who must sign and date the consent form in the presence of the subject. The communications with the subject regarding informed consent process (initial and subsequent) should be documented in the medical record.

5. Study Procedures

Study Assessments

Visit 1- Baseline Assessment

The following information will be collected at the time of enrollment:

- Informed Consent
- Medical History & Demographics
- Patient Outcomes: Subject to complete VAS, VR-12, KOOS, Lysholm and SANE prior to injection.
- Range of Motion Assessment: Measurement taken using goniometer.

Visit 2- Randomization & Procedure

- **Inclusion/Exclusion review**
- **Randomization**
- Procedure: For patients with current knee effusion, the investigator will drain the effusion prior to the injection. For subjects that do not exhibit any signs of knee effusion, the investigator will proceed with the injection. Study subjects will be randomized to receive a cortisone or BioDRestore injection. Subjects will be blinded to the assignment. Prior to the injection, the area will be prepared with sterile solution and numbing agent. Next, an injection of one of the following treatments, dependent on randomization, will be injected into the articular space of the knee:

  -2 cc of 40 mg/ml Kenalog with 3 cc of saline
  -2 cc BioDRestore with 3 cc of saline

  Knee arthrocentesis (for procedure, see below under "Follow-up Visits"): The study doctor will attempt to perform a knee aspiration to provide a delta value for the assay.

Follow-Up Visits (6WK, 3M, 6M, 12M)

The following information will be collected at each follow-up visit:

- Patient Outcomes: Subject to complete VAS, VR-12, KOOS, Lysholm, and SANE scales
- **6-month only, subject will return to the clinic for the following**:
    - Range of motion assessment
    - Knee arthrocentesis (aspiration): The area will first be prepared with sterile solution and numbing agent. Using a 10-mL syringe, obtain at least 0.25mL of synovial fluid via a parapatellar approach. A knee aspiration attempt will be made on all subjects that produced an adequate sample at baseline prior to the injection. Upon completion, the syringe will be labeled and transported to the Clemson Bioengineering Laboratory of Orthopaedic Tissue Regeneration & Orthobiologics lab for analysis.
    - Aspirate analysis: Enzyme linked immunosorbent assay (ELISA) will be performed on synovial fluid aspirated from the knees of study patients at 6 months post-injection to determine if there are quantitative differences in soluble mediators and products of osteoarthritis. Briefly, synovial fluid samples will be evaluated in duplicate for inflammatory (interleukin-1 beta; IL-1β and tumor necrosis factor-alpha; TNF-α), anti-inflammatory (interleukin-1 receptor agonist; IL-1RA and interleukin-10; IL-10), pain (prostaglandin-E2; PGE_2) and soluble signals which indicate cartilage damage (S100A8 and S100A9 proteins, respectively).

      Briefly, frozen (-80^{o}C) samples will be thawed and analyzed using a bicinchoninic acid assay (BCA) to normalize for total protein content. Samples will be diluted accordingly using calibrator diluent supplied with ELISA kits. ELISA will be performed according to manufacturer's protocols and well plates will be analyzed optically on a μ-Quant microplate reader. Concentrations will be determined using a standard curved developed from known concentrations of supplied analyte. Experimental sample analyte concentrations (ng/ml) will be plotted on histograms and group mean concentrations ± standard deviation will be calculated for each experimental group.
- **12-month only, subject will return to the clinic for the following**:
    - Range of motion assessment
    - Radiographs of affected knee
- Allowed Concomitant Medications and Prohibited Treatments
    - Concomitant Medications: Patients are allowed acetaminophen and/or ibuprofen for the first 6 months following treatment.
    - Prohibited Treatments: Oral steroids, steroid injections and Viscosupplementation are not permitted for the first 6 months of the study in the treated knee.

6. Risk Analysis

Potential Risks

Mild pain and discomfort at the injection site are normal and expected reactions. While rare, complications may occur due to either the cortisone injection or study injection. These include the following:

- Infection
- Post-injection flare
- Localized subcutaneous or cutaneous atrophy
- Skin discoloration
- Stiffness

Potential Benefits

Participation in this study may offer no benefit to subjects. However, it is possible that the use of BioDRestore will result in better outcomes than corticosteroid when injected intra-articularly in patients with knee OA.

Study subjects will receive a $50 stipend for each study visit for a total of $300 if all visits are completed.

7. Adverse Events

Definitions

An adverse event is defined as any untoward medical occurrence in a clinical investigation in which a subject is administered a study device and which does not necessarily have a causal relationship with the device. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or an abnormal radiographic finding), symptom, or disease temporally associated with the use of study device, whether or not related to the study device. The following are specific definitions of adverse events:

Adverse Event (AE) — any untoward medical occurrence in a subject, regardless if there is a relationship between the AE and the device.

Adverse Reaction (AR) - The FDA requires, per 21CFR 1271.350(a), the reporting of certain adverse reactions related to implantation, transplantation, infusion or transfer of an HCT/P. For tissue products, an Adverse Reaction is any unintended response, including a communicable disease, in the recipient of a human tissue or cell product implantation or transplantation. An Adverse Reaction is considered serious (SAR) if it meets the criteria of a Serious Adverse Event (see below).

Serious Adverse Event (SAE) — an adverse event that:

- leads to a death
- leads to a serious deterioration in the health of a subject that results in a life-threatening illness or injury
- results in a permanent impairment of a body structure or a body function
- requires in-subject hospitalization or prolongation of existing hospitalization
- results in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- results in congenital anomaly/birth defect

Treatment for Adverse Events

In the event of an adverse event, the investigator and/or other professional personnel in attendance will provide whatever appropriate medical treatment is indicated for the problem.

Documentation of Adverse Events

All adverse events will be documented in the source documentation. Beginning after the study procedure has taken place, all AE's, including those measured, observed or volunteered, will be recorded on the applicable case report form. The investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports)

relative to the event being reported. The investigator will then record all relevant information regarding an AE onto the study CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs and symptoms.

When reporting an AE, the investigator will evaluate the event for duration, intensity, relationship and outcome.

Examples of an AE:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- A new condition detected or diagnosed after study device administration even though it may have been present prior to the start of the study.
- Pre- or post-procedure events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a subject's previous treatment regimen).

An AE Does NOT Include:

- Medical or surgical procedures. The medical condition that leads to the procedure is the AE.
- Hospital admissions where an untoward medical occurrence did not occur.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- The condition/indication being studied or expected progression, signs, or symptoms of the condition/indication being studied unless more severe than expected for the subject's condition.
- Post-operative findings of swelling or pain within two (2) weeks of the initial procedure, unless deemed by the physician as of greater severity than expected.

Follow-Up of Adverse Events

After the initial AE report, the investigator is required to proactively follow each subject until the event resolves. All AEs documented at a previous visit that are designated as ongoing will be reviewed at subsequent visits/contacts.

Adverse events will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a subject experiencing a critical adverse event is treated successfully and stabilized even though he/she may continue to experience lingering sequelae that may never resolve), until the subject is lost to follow-up, or until it is agreed that further follow-up of the event is not warranted (e.g. non-serious, study therapy unrelated, mild or moderate adverse events ongoing at the subject's final study visit).

8. Reporting of Adverse Events

Investigator Adverse Event Reports

Investigators are responsible for reviewing all SAEs and determining the relationship to the treatment and documenting on the appropriate CRF. All SAEs must be reported by the investigator to the IRB as soon as possible, but no later than ten (10) working days after learning of the event. The investigator must submit a detailed report that will identify the description of symptoms, classification of the event, date of onset, severity, treatment, and outcome. Supporting medical records may be obtained as an adjunct to an adverse event report and placed in the subject's study file.

All AEs will be categorized as mild, moderate or severe based on the following definitions:

Mild: The subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or wellbeing.

Moderate: The subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.

Severe: The adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or wellbeing. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

Should an AR or SAE occur, an investigator must submit to DermaSciences and to the reviewing IRB a report of the event as soon as possible, but in no event later than 48 hours after the investigator first learns of the AR or SAE.

Reported ARs and Serious Adverse Events will be reviewed and investigated per Standard Operating Procedures. Upon a receipt and evaluation of an AR or SAE, Derma Sciences will report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after receipt of first notice of the AR or SAE. Thereafter, the Sponsor will submit such additional reports concerning the effect per FDA and/or IRB requests.

9. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject and each assessment in the protocol (source documents). Source documents include all information in original records and certified copies of original records of clinic findings, observations or other activities in the study necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (e.g., hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection and shipment records, research subject files, etc.)

10. Disclosure of Data and Data Security

Data Security and Confidentiality

The clinical data obtained in this study will be kept private. In any sort of published report, there will be no identifying information. Records for this study may be reviewed

by the IRB and/or other government agencies may inspect and photocopy all medical records applicable to involvement in this study.

Participating subjects will be asked to sign a consent form that includes an authorization to use and/or disclose personal health information. Subjects are free to refuse authorization to transfer personal information. If the subject chooses not to agree to this authorization, the subject is not eligible to participate in the study. Personal information (including sensitive personal health information, such as medical history) if relevant to the study will be reviewed, collected in a computer database, stored in electronic or manual files, audited, and / or otherwise processed by the investigator, regulatory agencies, and other persons and/or agencies as required by law or allowed by applicable regulations.

11. Statistical Procedures

11.1 Sample Size Estimate

To determine sample size, we powered the study (a-priori) for the primary outcome measures of VAS, VR-12, KOOS, Lysholm, and SANE scales at baseline, 6-week, 3-month, 6-month, and 12-month post-injection time periods. Assuming normal distributions among the 2 independent groups' 5 time-points for 2 groups and five outcome measures, and assuming an effect size of 0.20 (small) based on between group differences we constructed a sample size estimation using a Multivariate Analysis of Variance (MANOVA). Measuring global effects, with an expected 80% power, and a standard error of probability of 0.05, we estimate the need for a minimum sample size of 70 for statistical significance (~35 per group). To account for a 20% drop-out rate, a sample size of 84 subjects will be recruited. We will employ intention to treat and a chains equation, multiple imputation method in which we will assign predictor, structural and impute variables. Further, we will not oversample characteristics within each group for drop-outs.

11.2 Data Analyses

Descriptive statistics will be used to describe both groups at baseline. Appropriate tests of differences will be used to compare baseline differences in descriptive statistics, pain, range of motion, etc., between the two groups (e.g., t-tests and chi-square). Adverse events, including severity of these events will be captured and compared between the two groups. A Multivariate Analysis of Variance (MANOVA) will be used to measure differences between the targeted outcome measure at each of the given timepoints (baseline, 6-week, 3-month, 6-month, and 12-months post-injection time periods). A MANOVA investigates the effects of a categorical predictive variable (groups) on 2 or more continuous outcomes, which are correlated and represented by a vector of dependent variables. For all analyses, a p value of <0.05 will be considered statistically significant.

12. Bibliography

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