Study Protocol

STUDY NUMBER(S): AIOA001

PROTOCOL(S) TITLE: A PHASE 2B, PROSPECTIVE, DOUBLE-BLINDED, RANDOMIZED CONTROLLED TRIAL OF THE MICRONIZED dHACM INJECTION AS COMPARED TO SALINE PLACEBO INJECTION IN THE TREATMENT OF OSTEOARTHRITIS OF THE KNEE

NCT: 03485157

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SYNOPSIS

Name of Investigational Product: Allogeneic Micronized Dehydrated Human Amnion/Chorion Membrane (Micronized dHACM), a.k.a. AmnioFix Injectable
Study Design: A Phase 2B, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee
Indication: Knee osteoarthritis (OA)
Objective: To determine the safety and effectiveness of micronized dHACM as compared to the 0.9% Sodium Chloride Injection, USP placebo control for the treatment of knee osteoarthritis
Sample Size: Approximately 466 subjects will be enrolled in this study. Subjects to be randomized 1:1 in treatment arms.
Study Plan: The estimated enrollment period is 26 months. Each subject will receive 1 injection and be evaluated for efficacy and safety during a 12-month observation period. A second injection (open-label access to micronized dHACM) will be offered to all subjects at the 180-day, 270-day, and 365-day time points, see open-label access section below; it may only be used once. The study is expected to be completed within 44 months, inclusive of enrollment and follow-up for all subjects.
Procedures and Assessments: • Treatment (approx. 1 day): Screening, pre-procedure evaluation, injection procedure, baseline evaluation. • Clinical Follow-up (365-545 days): Routine follow-up with physical examination; pain, function, and quality of life measurements: Visual Analog Scale (VAS) for Pain, VAS for Satisfaction, Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, and Knee injury and Osteoarthritis Outcome Score (KOOS) will be evaluated at baseline, 30 days, 60 days, 90 days, 180 days, 270 days and 365 days after the initial treatment, and at time of open-label access and 30 days, 60 days, 90 days, and 180 days following the second injection should the subject elect to receive the open-label access treatment. Subject pain diaries will be completed at predefined intervals. • Safety Follow-up (365-545 days): Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Adverse Events will be evaluated at 30 days, 60 days, 90 days, 180 days, 270 days and 365 days after the initial treatment, and at time of open-label access and 30 days, 60 days, 90 days, and 180 days following the second injection should the subject elect to receive the open-label access treatment.
Primary Efficacy Endpoints (VAS for Pain and Total WOMAC): The co-primary efficacy endpoints are: • The change in VAS score for pain between baseline and Day 90 • The change in WOMAC osteoarthritis index total score (Total WOMAC score) between baseline and Day 90
Primary Safety Endpoint: The primary safety endpoint is the proportion of product-related Adverse Events (AEs), Serious Adverse Events (SAEs), and unanticipated adverse events throughout the study.
Secondary Endpoints: The secondary efficacy endpoints for this study are: • Change in VAS score for pain between baseline and 180 days • Change in Total WOMAC score between baseline and 180 days

Exploratory Endpoint:
For the cohort of subjects in the main phase of the study, i.e. who did not receive or have not yet received an open-label injection, the following exploratory endpoints will be assessed:

- Change in VAS score for pain between baseline and i-day (with i=30, 60, 270, and 365 days)
- Change in Total WOMAC score between baseline and i-day (with i=30, 60, 270, and 365 days)
- Change in pain, stiffness, and physical function WOMAC subscale scores between baseline and i-day (with i=30, 60, 90, 180, 270, and 365 days)
- Change in VAS score for satisfaction between baseline and i-day (with i=30, 60, 90, 180, 270, and 365 days)
- Change in KOOS scores between baseline and i-day (with i=30, 60, 90, 180, 270, and 365 days)
- Patient pain diary endpoints will be collected and summarized across applicable time points

For the cohort of subjects in the extension phase, i.e. who received the open-label injection and are within the period after the open-label injection, the following endpoints will be collected and summarized across applicable time points: VAS score for pain, Total WOMAC, WOMAC subscales for pain, stiffness and physical function, VAS score for satisfaction, KOOS, and pain diary entries.

Inclusion Criteria

All subjects enrolled must meet all the following criteria:

1. Age $\geq$ 21 and $\leq$ 80 years
2. Subject has a diagnosis of osteoarthritis (OA) defined as Grade 1 to 3 on the Kellgren Lawrence grading scale
3. Subject is willing and able provide informed consent and participate in all procedures and follow-up evaluations necessary to complete the study
4. Subject must have a VAS pain scale greater than 45

Exclusion Criteria

Any potential subjects meeting any of the following criteria will be excluded from enrollment and subsequent randomization.

1. Subject has a diagnosis of osteoarthritis (OA) defined as Grade 4 on the Kellgren Lawrence grading scale
2. BMI greater than 40 kg/m^2
3. Subject has active infection at the injection site
4. Symptomatic OA of the contralateral knee or of either hip that is not responsive to acetaminophen (Tylenol®) and requires other therapy.
5. Subject has rheumatoid arthritis, psoriatic arthritis, or have been diagnosed with any other disorders that is the primary source of their knee pain, including but not limited to: osteonecrosis, radiculopathy, bursitis, tendinitis, tumor, cancer
6. Subject has documented history of gout or pseudo-gout
7. Subject has autoimmune disease or a known history of having Acquired Immunodeficiency Syndromes (AIDS) or HIV
8. Subject has received any of the following to the target knee:
    a. Intra-articular hyaluronic acid (HA) injection within 12 weeks prior to screening
    b. Steroid or platelet rich plasma (PRP) injection within 12 weeks prior to screening
    c. Has had or is planning to have major surgery or arthroscopy in the target knee within 26 weeks of treatment
    d. History of a total knee arthroplasty
9. Subject has used an investigational drug, device or biologic within 12 weeks prior to treatment
10. Subject has a history of immunosuppressive or chemotherapy in the last 5 years
11. Subject has had prior radiation at the site
12. Subject is currently taking anticoagulant therapy (excluding Plavix or Aspirin)
13. Subject is pregnant or plans to become pregnant within 365 days of treatment
14. Subject has any significant medical condition that, in the opinion of the Investigator, would interfere with protocol evaluation and participation
15. Subject is a worker's compensation patient
16. Subject is a prisoner

Open-Label Access:

All study subjects will be eligible to receive one injection of micronized dHACM at either of the Day 180, Day 270, and Day 365 time points. The investigators and subjects will remain blind to the initial treatment assignment at this time, and until the study is unblinded.
Subjects who receive the open-label access treatment will continue to be followed for 180 days after this second injection, regardless of the time at which treatment was received.

Statistical Methods:

The change in VAS score for pain and Total WOMAC score between baseline and Day 90 (primary endpoints) and between baseline and Day 180 (secondary endpoints) will be compared between the treatment arms using an ANOVA with treatment as a fixed effect and study site as the block effect.
For the purposes of this protocol, we will be examining knee osteoarthritis. The hypothesis to be tested is to confirm that the use of micronized dHACM offers a statistically significant advantage over placebo control.
Efficacy and safety data will be submitted for evaluation following the completion of the study follow-up.