Osteoarthritis of the Knee: Interim, Exploratory Analysis of Treated and Placebo-Controlled, Phase 1 Study

**Background**

Osteoarthritis (OA) is a major cause of activity limitation and physical disability in adults. OA accounts for 6.3% of all years of life lost to disability in the U.S. making it disease burden the third greatest in the nation and more than diabetes and other degenerative and infectious diseases (5.0%), diabetes (3.3%), HIV (1.8%), and rheumatoid arthritis (1.3%).

**Methods (continued)**

- **Sample size:** 20 subjects (randomized 4:1, 16 active; 4 placebos) per dosing cohort was selected for this exploratory study.
- **Placebo** was diluent containing 0.5% carbopol/ethoxylate sodium and 0.03 mg polysorbate 80 in p H 7.4 phosphate buffered saline.
- **Subjects were given** a single, intra-articular injection in the knee joint on Treatment Day 1 and participated in a follow-up period of 24 weeks.
- **Knee MRIs** were obtained with an 16 channel knee coil on a 3.0T MRI machine using a standard diagnostic protocol (resolution 0.1 – 0.4 mm). MRI scans were collected at the baseline visit (which could occur 28 days prior to study injection) and again at Weeks 12 and 24.
- **As a safety assessment, MRI scans were used** to monitor the presence of focal or diffuse bone marrow edema (BME) in all subjects.

**Average cartilage thickness over covered subchondral bone was reported for 4 compartments:**

- **Medial femoral condyle**
- **Medial tibial plateau**
- **Lateral femoral condyle**
- **Lateral tibial plateau**

**To determine average cartilage thickness, the cartilage thickness between the subchondral bone area (green contour, shown in the example below) and the articular cartilage surface (magenta) was measured at numerous (>400-2000) locations in both directions in the parts covered by cartilage (AB) and averaged. Measurements were performed in 3D.**

OA was defined as the presence of cartilage degradation and osteophyte formation. The presence of subchondral bone changes was not used as an inclusion criterion. Instead, OA was defined in a non-invasive manner using whole-body MRI scanning.

In OA, cartilage is damaged by articular cartilage, subchondral bone alterations and varying degrees of synovitis.

To our knowledge, this is the first study to report a cartilage imaging endpoint for an OA therapy. This endpoint is more sensitive than radiographic outcomes and therefore provides a new tool for early OA treatment development.

**Methods**

- **Image provided by Dr Chondrometrics GmbH (Ainring, Germany)**
- **Bone Marrow Edema (BME)**

**Results**

- **Joint Space Width by Radiograph at Week 24**
- **MRI** was the primary method utilized to examine BME, which the FDA defined as a safety outcome in this phase 1 trial.
- **BME** stayed the same for most subjects from baseline to Week 12. For some subjects in both treatment (N=4) and Placebo (N=3) groups, BME worsened (more focal). 4 subjects in the treatment groups showed improved BME in focal (more focal, and diffuse); focal, and diffuse focal. This interim BME imaging data suggest that a single intra-articular injection of SM4690 into the knee of OA subjects resulted in no appreciable change in BME compared to Placebo.
- Although exploratory imaging results in this phase 1 trial suggest that the 0.23 mg dose is less effective than the 0.03 mg and 0.07 mg doses, it should be noted that the 0.23 mg cohort consisted of the highest percentage of K-L Grade 3 subjects.
- **Radiography** is currently the "gold standard" for knee OA trials. However, while MRI has been an accepted regulatory analysis for exploratory outcomes, it can provide comprehensive information on articular tissue pathology than radiography.
- Although overall sample size is too small to form definitive conclusions, exploratory analyses of MRI outcomes suggest:
  - Treated subjects appeared to show no substantial degradation in cartilage thickness at Week 12.
  - The area of thinnest cartilage showed a possible trend towards increase in the 0.03 mg and 0.07 mg cohorts at Week 12.
- **Radiographs measuring the change from baseline in Week 24 in JSW show no statistically significant changes in the 0.03 mg, 0.07 mg cohort, and a decrease in the 0.23 mg cohort, with the Placebo group also exhibiting a decrease.
- **MRI** offers whole body data required to determine feasibility of this imaging technique for OA. However, the MRI safety analyses from this interim analysis demonstrated no worsening of bone edema in knee OA subjects treated with SM4690.
- **Preliminary safety outcomes observed from MRI analyses, and efficacy outcomes from radiographic and clinical data (reported in Poster 31), support the ongoing development program for SM4690 (NCT02536833, currently enrolling).**

**References**