Safety, Clinical, and Imaging Outcomes of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM4690) in the Treatment of Osteoarthritis of the Knee: Exploratory Analysis of Results From a 24 Week, Randomized, Double-Blind, Placebo-Controlled, Phase I Study

Yusuf Yazici1, Timothy E. McAlindon2, Roy Flieshaerman3, Alan Gibbons4, Nancy E. Lane5, Alan J. Koltz6, Sharmila Majumdar6, Viveka Strand7, Christopher J. Swaingering8, Anita DiFranco9, Jeseyran N. R. Tambali10, John Hood10 and Marc C. Hochberg11
1Samumed, San Diego, CA, 2Tufts Medical Center, Boston, MA, 3University of Texas Southwest Medical Center, Dallas, TX, 4Wish Medical College and Hospital for Special Surgery, New York, NY, 5University of California Davis Medical Center, Davis, CA, 6Alliance for Clinical Research at Duke University, Durham, NC, 7San Francisco, Stanford Pai, Palo Alto, CA, 8University of Maryland School of Medicine, Baltimore, MD

Background

Osteoarthritis (OA) is a major cause of activity limitation and physical disability in adults, and it has a significant effect on quality of life, costs and productivity. The global disease burden of hip and knee OA ranks #1 of 219 conditions, and knee OA has a global prevalence of 3.6%.1

To date, there are no approved disease modifying agents for knee OA.

The Wnt signaling pathway is known to play a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.2

In osteoarthritic joints, increased Wnt signaling leads to cartilage destruction, messel道歉ure production and directly leads to OA.3

The effect of the study was to evaluate the safety and tolerability of SM4690 administered by LA injection into a target knee joint to subjects with severe symptomatic OA. Exploratory efficacy analyses were also performed.

Methods

This was a 4-arm, double-blind, placebo-controlled, single-dose, dose-escalation safety study of a Wnt pathway inhibitor in subjects with knee osteoarthritis. Subjects

Subjects aged 50-75 years with Western Ontario and McMaster Universities Arthritis Index (WOMAC) Total score ≥40; Knee Lawrence-Grade 2 or 3; willing to enroll in pain medications for hours prior to the last injection; BMI >40, and no treatment with steroids within 2 months of hyaluronic acid derivatives within 6 months prior to injection were eligible for the study.

The dosing sequence included the following concentration levels: 0.03 mg, 0.07 mg, and 0.23 mg SM4690 per mL injection. A sample size of 10 subjects randomized (4.1, 16.2, 4.1) per dose cohort was selected for this exploratory study.

Safety pharmacology (PK), biomarker, and pre-specified efficacy data were collected at baseline and during the 24-week follow-up period.

Safety: Adverse events (AEs), concomitant medications, clinical laboratory sampling, medical history, vital signs, QOL, hip bone density (DXA) analysis, thickness of cartilage via QCT, and evaluation of bone marrow lesions via MRI.

PK: Samples collected 0, 4, 24, and 72 hours post dose, and 4 weeks and 12 weeks.

Biomarkers: Cartilage oligomeric protein (COMP), N-terminal propeptides of procollagen type 1 (PINP), and C terminal isopeptide of type I collagen (ICT3C).

Efficacy: WOMAC total score, WOMAC Function Pain subscore, pain VISUAL, Physician Global Assessment of Osteoarthritis (KDR), and radiographs of joint space width.

All AEs reported in this study were considered related to study medication. Investigator opinion regarding the relationship of AEs was also collected for informational purposes and presented here.

Efficacy assessments were used to determine the percentage of OMERACT-OARSI “responders” (responders). “Strict” responders were defined as subjects exhibiting either WOMAC Function subscore improvement of ≥20% with a corresponding WOMAC Function subscore improvement of ≥0.2 points (scaled to 0-100); WOMAC Pain subscore improvement of ≥20% with a corresponding WOMAC Pain subscore improvement of ≥0.2 points (scaled to 0-100).

Exploratory efficacy of outcomes obtained using an intention-to-treat (ITT) analysis for continuous variables. Pairwise comparisons were made using 2-tailed t-tests. Paired samples (i.e. matched) were compared using Wilcoxon signed rank test.

Results

Subject Characteristics [MTT]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [Mean (SD)]</td>
<td>63.4 (6.6)</td>
<td>60.8 (5.8)</td>
<td>63.1 (4.9)</td>
<td>64.1 (5.8)</td>
</tr>
<tr>
<td>BMI [Mean (SD)]</td>
<td>31.4 (4.8)</td>
<td>38.6 (4.6)</td>
<td>31.8 (4.6)</td>
<td>26.7 (5.3)</td>
</tr>
<tr>
<td>Female [%]</td>
<td>10 (38.0)</td>
<td>13 (77.8)</td>
<td>10 (62.5)</td>
<td>6 (35.0)</td>
</tr>
<tr>
<td>Race [%%]</td>
<td>White (94)</td>
<td>14 (92.3)</td>
<td>14 (92.3)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Asian (12)</td>
<td>1 (7.7)</td>
<td>1 (7.7)</td>
<td>2 (12)</td>
<td>1 (6.2)</td>
</tr>
<tr>
<td>African-American (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 1. Subject characteristics by treatment arm.

OMERACT-OARSI Responders – Weeks 12 and 24

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subscore A [%]</td>
<td>56%</td>
<td>76%</td>
<td>44%</td>
<td>36%</td>
</tr>
<tr>
<td>Subscore B [%]</td>
<td>56%</td>
<td>76%</td>
<td>44%</td>
<td>36%</td>
</tr>
<tr>
<td>Subscore C [%]</td>
<td>56%</td>
<td>76%</td>
<td>44%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Table 2. OMERACT-OARSI responder rates (Mean ± Standard Deviation) for each treatment arm.

Safety

Adverse Events

AEs were reported in all treatment groups. The most common AEs were moderate to severe joint pain, injection site irritation, and rhinitis.

Pharmacokinetics

Mean peak concentration (Cmax) was observed at Week 12 for all treatment groups. The mean area under the curve (AUC) was 20-0 mg/L h (0-24 h) for all treatment groups.

Discussion

These data from the phase 1 study suggested that a single intra-articular injection of the novel Wnt inhibitor SM4690 into the knee of OA subjects appeared safe, well-tolerated, and potentially effective in improving function, pain, and joint space width.

Conclusion

This phase 1 study was not powered to detect any statistically significant differences between treatment groups and placebo. However, the data suggested that subjects treated with SM4690 were more likely to achieve an OMERACT-OARSI strict response than placebo. Since the study was not powered to achieve 70% of 0.07 mg and 20% of 0.23 mg of placebo cohort at week 12 (90% power, r = 0.5), and 70% of 0.07 mg or 35% of 0.23 mg of placebo at week 24 (90% power, r = 0.44), additional comparison of the mean and median change from baseline for Physician Global Assessment of Disease Activity and WOMAC Total Score consistent improvement in the 0.23 mg and 0.7 mg SM4690 groups, suggesting a uniform effect across all doses.

This study supported the development of an ongoing phase 2 study (NCT02353333) designed to further investigate additional safety, dose response, and efficacy in subjects with knee OA.

References