Results from a Phase 2B Trial of SM04690, a Novel Intra-articular Wnt Pathway Inhibitor for the Treatment of Knee Osteoarthritis

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Disclosures

- All authors are employees, shareholders, or consultants of Samumed, LLC
Upregulated Wnt signaling contributes to OA progression

Increased Wnt signaling:

- Progenitor cells in the synovium and subchondral bone form osteoblasts rather than chondrocytes \(^1-3\)
- Pro-inflammatory cytokines and catabolic enzymes that drive cartilage degradation and OA symptoms are increased \(^4-5\)


Figure adaptations: www.york.ac.uk and Bush J & Beier F. (2013) Nature Med.
OA: A disease of the whole joint

- Bone marrow
- Synovial membrane
- Articular cartilage
- Bone remodeling
- Synovitis
- Cartilage remodeling
- Joint capsule damage
- Meniscal tears or extrusion

Potentially affected by Wnt signaling
SM04690: A proposed treatment for knee OA

- A small-molecule, intra-articular Wnt pathway inhibitor in development for the treatment of knee OA¹,²
- In preclinical studies, SM04690 inhibited inflammation, decreased cartilage degradation, and regenerated cartilage¹
- In preclinical studies, SM04690 demonstrated sustained local exposure and no observable systemic toxicity¹,²
- In a previous phase 2a study, improvements in pain, function, and radiographic medial joint space width were observed in unilateral symptomatic and unilateral symptomatic without widespread pain subgroups (0.07 mg SM04690 dose, compared to placebo) at Week 52³

1. Deshmukh V, et al. (2017) OAC.
SM04690-OA-04: Objectives and endpoints

- **Primary objective:** Determine the effective dose(s) of SM04690 for the treatment of OA

- **Secondary objective:** Evaluate the safety and tolerability of SM04690

- **Primary endpoints:** Evaluate change from baseline compared to PBO at Week 24 in:
  1. OA pain in the target knee as assessed by the weekly averages of daily Pain Numeric Rating Scale (NRS)
  2. OA pain in the target knee as assessed by WOMAC Pain subscore
  3. OA function in the target knee as assessed by WOMAC Function subscore
  4. Medial joint space width (mJSW) as documented by radiograph of the target knee
SM04690-OA-04: Phase 2 study design

Clinical assessments: Daily Pain NRS, WOMAC Function, WOMAC Pain, Patient Global Assessment, Physician Global Assessment, KOOS, KOOS-PS, daily NSAID

Imaging: Knee X-ray

Safety assessments: AEs, Vital signs, Physical exam, Laboratory panels
### Key Inclusion Criteria

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-80 years, good health</td>
<td><strong>BMI &gt;35</strong></td>
</tr>
<tr>
<td>Ambulatory (aids allowed if needed &lt;50%)</td>
<td>Major surgery in target knee within 12 months</td>
</tr>
<tr>
<td>Clinical and radiological ACR diagnosis of primary femorotibial OA in target knee &gt;6 months</td>
<td>IA steroids within 2 months</td>
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<tr>
<td></td>
<td>Hyaluronic acid, PRP, stem cell therapies within 6 months</td>
</tr>
<tr>
<td>Kellgren-Lawrence Grade 2/3 in target knee</td>
<td>Target knee effusion requiring aspiration within 3 months</td>
</tr>
<tr>
<td><strong>Daily pain diary average ≥4 and ≤8 on 0-10 NRS in target knee at least 4 of 7 days</strong></td>
<td>Opioids &gt;1x/week within 12 weeks screening</td>
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<td></td>
<td>Subjects not on stable NSAID regimen</td>
</tr>
<tr>
<td><strong>Daily pain diary average &lt;4 on 0-10 NRS in contralateral knee at least 4 of 7 days</strong></td>
<td>Any chronic condition not well controlled &gt;3 months</td>
</tr>
</tbody>
</table>
SM04690-OA-04: Patient disposition

2672 subjects screened

1972 subjects discontinued prior to randomization

700 subjects randomized

5 subjects discontinued prior to treatment

0.03 mg SM04690 116 subjects
- Completed n=107 (91.5%)
- Total DC: n=9 (8.5%)

0.07 mg SM04690 115 subjects
- Completed n=111 (95.7%)
- Total DC: n=4 (4.3%)

0.15 mg SM04690 116 subjects
- Completed n=105 (89.7%)
- Total DC: n=10 (9.5%)

0.23 mg SM04690 116 subjects
- Completed n=105 (90.5%)
- Total DC: n=11 (12.8%)

Placebo (Vehicle) 116 subjects
- Completed n=102 (87.2%)
- Total DC: n=14 (12.8%)

Sham 117 subjects
- Completed n=105 (89.7%)
- Total DC: n=12 (10.3%)

DC=discontinued
## SM04690-OA-04: Subject characteristics

### Full analysis set

<table>
<thead>
<tr>
<th></th>
<th>SM04690</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.15 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>116</td>
<td>115</td>
<td>115</td>
<td>116</td>
<td>116</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Age at Consent (years)*</td>
<td>57.9 (7.9)</td>
<td>59.9 (8.6)</td>
<td>58.4 (8.3)</td>
<td>58.5 (9.0)</td>
<td>60.1 (9.0)</td>
<td>59.0 (8.0)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))*</td>
<td>29.2 (3.8)</td>
<td>29.1 (3.6)</td>
<td>29.4 (4.1)</td>
<td>28.5 (4.4)</td>
<td>28.6 (4.3)</td>
<td>29.0 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>76 (65.5%)</td>
<td>66 (57.4%)</td>
<td>69 (60.0%)</td>
<td>61 (52.6%)</td>
<td>64 (55.2%)</td>
<td>70 (59.8%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>85 (73.3%)</td>
<td>83 (72.2%)</td>
<td>84 (73.0%)</td>
<td>89 (76.7%)</td>
<td>90 (77.6%)</td>
<td>86 (73.5%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>24 (20.7%)</td>
<td>22 (19.1%)</td>
<td>25 (21.7%)</td>
<td>21 (18.1%)</td>
<td>17 (14.7%)</td>
<td>24 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (4.3%)</td>
<td>5 (4.3%)</td>
<td>6 (5.2%)</td>
<td>5 (4.3%)</td>
<td>6 (5.2%)</td>
<td>3 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>KL Grade 3</td>
<td>63 (54.3%)</td>
<td>74 (64.3%)</td>
<td>68 (59.1%)</td>
<td>63 (54.3%)</td>
<td>72 (62.1%)</td>
<td>58 (49.6%)</td>
<td></td>
</tr>
<tr>
<td>Unilateral Symptomatic</td>
<td>59 (50.9%)</td>
<td>62 (53.9%)</td>
<td>63 (54.8%)</td>
<td>63 (54.3%)</td>
<td>61 (52.6%)</td>
<td>62 (53.0%)</td>
<td></td>
</tr>
<tr>
<td>Widespread Pain Negative</td>
<td>92 (79.3%)</td>
<td>93 (80.9%)</td>
<td>90 (78.3%)</td>
<td>93 (80.2%)</td>
<td>93 (80.2%)</td>
<td>94 (80.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean (SD) reported. Otherwise N (%) reported.
## SM04690-OA-04: Adverse events (AEs)
### Safety analysis set

<table>
<thead>
<tr>
<th>AE Reported ≥1%*</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.15 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
<th>Sham</th>
<th>Other</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>106</td>
<td>104</td>
<td>106</td>
<td>106</td>
<td>114</td>
<td>120</td>
<td>39</td>
<td>695</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>6 / 6 (5.7%)</td>
<td>8 / 7 (6.7%)</td>
<td>2 / 2 (1.9%)</td>
<td>12 / 9 (8.5%)</td>
<td>3 / 3 (2.6%)</td>
<td>7 / 7 (5.8%)</td>
<td>4 / 3 (7.7%)</td>
<td>42 / 37 (5.3%)</td>
</tr>
<tr>
<td><strong>Upper respiratory tract infection</strong></td>
<td>2 / 2 (1.9%)</td>
<td>5 / 5 (4.8%)</td>
<td>0 / 0 (0.0%)</td>
<td>3 / 3 (2.8%)</td>
<td>4 / 4 (3.5%)</td>
<td>5 / 4 (3.3%)</td>
<td>1 / 1 (2.6%)</td>
<td>20 / 19 (2.7%)</td>
</tr>
<tr>
<td><strong>Sinusitis</strong></td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (1.0%)</td>
<td>1 / 1 (0.9%)</td>
<td>3 / 3 (2.8%)</td>
<td>1 / 1 (0.9%)</td>
<td>4 / 4 (3.3%)</td>
<td>0 / 0 (0.0%)</td>
<td>11 / 11 (1.6%)</td>
</tr>
<tr>
<td><strong>Urinary tract infection</strong></td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (1.0%)</td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (0.9%)</td>
<td>4 / 4 (3.3%)</td>
<td>1 / 1 (2.6%)</td>
<td>10 / 10 (1.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Viral upper respiratory tract infection</strong></td>
<td>2 / 2 (1.9%)</td>
<td>2 / 2 (1.9%)</td>
<td>0 / 0 (0.0%)</td>
<td>1 / 1 (0.9%)</td>
<td>3 / 3 (2.6%)</td>
<td>1 / 1 (0.8%)</td>
<td>0 / 0 (0.0%)</td>
<td>9 / 9 (1.3%)</td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong></td>
<td>2 / 2 (1.9%)</td>
<td>2 / 2 (1.9%)</td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (0.8%)</td>
<td>0 / 0 (0.0%)</td>
<td>8 / 8 (1.2%)</td>
</tr>
<tr>
<td><strong>Bronchitis</strong></td>
<td>3 / 3 (2.8%)</td>
<td>1 / 1 (1.0%)</td>
<td>1 / 1 (0.9%)</td>
<td>1 / 1 (0.9%)</td>
<td>0 / 0 (0.0%)</td>
<td>0 / 0 (0.0%)</td>
<td>1 / 1 (2.6%)</td>
<td>7 / 7 (1.0%)</td>
</tr>
</tbody>
</table>

*#AE / #Subjects (%) reported.

### Subjects Reporting AEs
- 36 (34.0%) 40 (38.5%) 30 (28.3%) 32 (30.2%) 36 (31.6%) 39 (32.5%) 10 (25.6%) 223 (32.1%)

### Subjects Not Reporting AEs
- 70 (66.0%) 64 (61.5%) 76 (71.7%) 74 (69.8%) 78 (68.4%) 81 (67.5%) 29 (74.4%) 472 (67.9%)

### Serious AEs†
- 2 / 2 (1.9%) 0 / 0 (0.0%) 0 / 0 (0.0%) 2 / 2 (1.9%) 1 / 1 (0.9%) 0 / 0 (0.0%) 1 / 1 (0.9%) 6 / 6 (0.9%)

†All unrelated to SM04690.

Other: All subjects treated with dose of SM04690 not 0.03 mg, 0.07 mg, 0.15 mg, or 0.23 mg or PBO
Pain NRS [0-10] and Patient Global [0-100]
Actual scores (mean ± standard errors)

Statistical comparisons from baseline-adjusted ANCOVA versus placebo were conducted at 4-week intervals.

Data on x-axis is offset for visual clarity.

*SM04690 0.07 mg P<0.05  †SM04690 0.23 mg P<0.05
WOMAC Pain [0-100] and WOMAC Function [0-100]
Actual scores (mean ± standard errors)

Comparisons from baseline-adjusted ANCOVA versus placebo
Data on x-axis is offset for visual clarity

*SM04690 0.07 mg P<0.05  †SM04690 0.23 mg P<0.05
Medial Joint Space Width (mm)
Actual scores (mean ± standard errors)

mJSW (FAS)

Comparisons from baseline-adjusted ANCOVA versus placebo
Data on x-axis is offset for visual clarity
*SM04690 0.07 mg P<0.05  †SM04690 0.23 mg P<0.05
Phase 2b conclusions

- In this study, SM04690 showed statistically significant improvements from baseline in pain and function compared to PBO
  - All doses appeared safe and well tolerated
  - 0.07 mg and 0.23 mg appeared to be potentially efficacious doses
  - Further analyses of subject characteristics may refine target population
- Improvements seen in pain and function suggest that SM04690 has a potential role in the treatment of knee OA signs and symptoms
- Further investigation of SM04690 as a potential DMOAD with studies evaluating structure and morphology are underway
- Pivotal studies are planned
Thank you
Stratification based upon clinically relevant OA phenotypes:

- (A) 50% Unilaterally Symptomatic vs. (B) 50% Bilaterally Symptomatic

- (1) 80% WPI≤4 and Symptom Severity Question 2≤2 vs. (2) 20% WPI>4 and/or Symptom Severity Question 2>2