Treatment of Knee Osteoarthritis with SM04690 Improved WOMAC A1 “Pain on Walking” – Results from a 52 Week, Randomized, Double Blind, Placebo Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor

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DISCLOSURES

- Sarah Kennedy: Samumed, LLC employee and shareholder
- Heli Ghandehari: Samumed, LLC employee and shareholder
- Christopher Swearingen: Samummed, LLC employee and shareholder
- Jeyanesh Tambiah: Samummed, LLC employee and shareholder
- Marc Hochberg: Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Theralogix, LLC, Samumed, LLC
WOMAC question A1 commonly used as an endpoint in osteoarthritis (OA) trials

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee score
  - extensively used patient reported outcome measure
  - 24 items in 3 subscales: A = pain [5], B = stiffness [2], C = physical function [17]

- Question A1, walking pain on a flat surface
  - major symptom of tibio-femoral OA and differentiates from patello-femoral OA\(^1,2\)
  - multi-dimensional, incorporating pain and function
  - onset usually earlier than rest pain
  - used as a clinical trial endpoint for many intra-articular (IA) compounds in knee OA

WOMAC A1: ‘pain when walking on a flat surface’ question is multi-dimensional

• ‘How much pain have you had when walking on a flat surface?’
• ‘How much difficulty have you had when walking on a flat surface?’

Think about the pain you felt in your __________ (study joint) caused by the arthritis during the last 48 hours.

(Please mark your answers by putting an “X” in one of the boxes.)

QUESTION: How much pain have you had . . .

1. when walking on a flat surface?
   - No Pain
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Pain

2. when going up or down stairs?
   - No Pain
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Pain

3. at night while in bed? (that is - pain that disturbs your sleep)
   - No Pain
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Pain

4. while sitting or lying down?
   - No Pain
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Pain

5. while standing?
   - No Pain
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Pain

QUESTION: How much difficulty have you had . . .

8. when going down the stairs?
   - No Difficulty
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Difficulty

9. when going up the stairs?
   - No Difficulty
   - 0 1 2 3 4 5 6 7 8 9 10
   - Extreme Difficulty

10. when getting up from a sitting position?
    - No Difficulty
    - 0 1 2 3 4 5 6 7 8 9 10
    - Extreme Difficulty

11. while standing?
    - No Difficulty
    - 0 1 2 3 4 5 6 7 8 9 10
    - Extreme Difficulty

12. when bending to the floor?
    - No Difficulty
    - 0 1 2 3 4 5 6 7 8 9 10
    - Extreme Difficulty

13. when walking on a flat surface?
    - No Difficulty
    - 0 1 2 3 4 5 6 7 8 9 10
    - Extreme Difficulty
Knee OA, the Wnt pathway, and SM04690

• The Wnt pathway is upregulated in OA.\(^1,2\) Inhibition may regenerate and protect articular cartilage

• SM04690: an IA Wnt pathway inhibitor for potential treatment of knee OA
  – preclinical studies demonstrated inhibition of inflammation and cartilage degradation \textit{in vitro} and \textit{in vivo} compared with vehicle\(^3\)
  – phase 2 study demonstrated improvements in WOMAC Pain, Function, and radiographic medial joint space width compared to placebo (PBO) in clinically relevant subgroups for 0.07 mg dose at 52 weeks\(^4\)

• This post-hoc analysis evaluated SM04690 effects measured by WOMAC A1

2. Thomas RS, et al. (2011) \textit{Arthritis Res Ther.}
SM04690-OA-02: Phase 2 study design

2mL Injection at Day 1

- 0.03 mg SM04690 (n=112)
- 0.07 mg SM04690 (n=117)
- 0.23 mg SM04690 (n=109)
- Vehicle (PBO) (n=114)

Study Week: 0, 4, 13, 26, 39, 52/EOS

Follow Up

Primary objective: Change from baseline in WOMAC pain at Week 13

Clinical assessments: WOMAC Function, Pain; Patient and Physician Global Assessment; SF-36

Imaging: Fixed flexion knee X-ray with QuAP™ positioner

Safety assessments: Adverse events (AEs), Vital signs, Physical exam, Lab panels

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
Incidence of adverse events

<table>
<thead>
<tr>
<th>AE(s) Reported* &gt;2% [#AE / N(%)]</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>16 / 13 (11.7)</td>
<td>14 / 13 (11.4)</td>
<td>13 / 9 (8.7)</td>
<td>12 / 10 (9.3)</td>
<td>61 / 49 (10.8)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>5 / 3 (2.7)</td>
<td>4 / 4 (3.5)</td>
<td>2 / 2 (1.9)</td>
<td>6 / 5 (4.6)</td>
<td>17 / 14 (3.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 / 5 (4.5)</td>
<td>2 / 2 (1.8)</td>
<td>1 / 1 (1.0)</td>
<td>3 / 3 (2.8)</td>
<td>12 / 12 (2.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 / 0 (0.0)</td>
<td>4 / 4 (3.5)</td>
<td>4 / 4 (3.8)</td>
<td>3 / 3 (2.8)</td>
<td>11 / 11 (2.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 / 4 (3.6)</td>
<td>3 / 3 (2.6)</td>
<td>3 / 3 (2.9)</td>
<td>0 / 0 (0.0)</td>
<td>11 / 11 (2.4)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>4 / 3 (2.7)</td>
<td>2 / 2 (1.8)</td>
<td>3 / 3 (2.9)</td>
<td>5 / 3 (2.8)</td>
<td>14 / 11 (2.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 / 0 (0.0)</td>
<td>6 / 3 (2.6)</td>
<td>2 / 2 (1.9)</td>
<td>4 / 4 (3.7)</td>
<td>13 / 10 (2.2)</td>
</tr>
<tr>
<td>Joint effusion</td>
<td>5 / 4 (3.6)</td>
<td>2 / 2 (1.8)</td>
<td>1 / 1 (1.0)</td>
<td>2 / 2 (1.9)</td>
<td>10 / 9 (2.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1 / 1 (0.9)</td>
<td>2 / 2 (1.8)</td>
<td>1 / 1 (1.0)</td>
<td>5 / 5 (4.6)</td>
<td>9 / 9 (2.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 / 2 (1.8)</td>
<td>2 / 2 (1.8)</td>
<td>3 / 2 (1.9)</td>
<td>3 / 3 (2.8)</td>
<td>10 / 9 (2.0)</td>
</tr>
</tbody>
</table>

0.03 mg (n=111) 0.07 mg (n=114) 0.23 mg (n=104) Placebo (n=108)

| Subjects Reporting AE(s) [N(%)] | 61 (55.0) | 65 (57.0) | 47 (45.2) | 53 (49.1) |
| Subjects Reporting No AE(s) [N(%)] | 50 (45.0) | 49 (43.0) | 57 (54.8) | 55 (50.9) |
| Subjects Reporting SAE(s) [#AE / N(%)] | 7/5 (4.5) | 12/4 (3.5) | 5/4 (3.8) | 3/3 (2.8) |

No SAEs were deemed related to study drug by PI.

*All AEs deemed related to drug per protocol.
### SM04690-OA-02: Demographics

<table>
<thead>
<tr>
<th></th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>112</td>
<td>117</td>
<td>110</td>
<td>116</td>
<td>455</td>
</tr>
<tr>
<td><strong>Age (years) [mean (SD)]</strong></td>
<td>59.0 (9.0)</td>
<td>60.0 (8.2)</td>
<td>61.3 (8.7)</td>
<td>60.7 (8.9)</td>
<td>60.3 (8.7)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) [mean (SD)]</strong></td>
<td>29.8 (4.8)</td>
<td>30.8 (4.7)</td>
<td>29.6 (4.5)</td>
<td>29.2 (4.4)</td>
<td>29.9 (4.6)</td>
</tr>
<tr>
<td><strong>Female [n(%)]</strong></td>
<td>68 (60.7%)</td>
<td>60 (51.3%)</td>
<td>68 (61.8%)</td>
<td>72 (62.1%)</td>
<td>268 (58.9%)</td>
</tr>
<tr>
<td><strong>KL grade 3 [n(%)]</strong></td>
<td>74 (66.1%)</td>
<td>74 (63.2%)</td>
<td>70 (63.6%)</td>
<td>74 (63.8%)</td>
<td>292 (64.2%)</td>
</tr>
<tr>
<td><strong>Unilateral Symptomatic [n(%)]</strong></td>
<td>45 (40.2%)</td>
<td>35 (29.9%)</td>
<td>45 (40.9%)</td>
<td>39 (33.6%)</td>
<td>164 (36.0%)</td>
</tr>
<tr>
<td><strong>Unilateral Symptomatic WP- [n(%)]</strong></td>
<td>34 (30.4%)</td>
<td>29 (24.8%)</td>
<td>33 (30.0%)</td>
<td>32 (27.6%)</td>
<td>128 (28.1%)</td>
</tr>
</tbody>
</table>
SM04690-OA-02: Analysis groups

- **Intention to treat population (ITT, n=455):** All randomized subjects
  - contra-lateral knee pain threshold not limited at enrollment
- **Unilateral Symptomatic (UNI, n=164):**
  - prespecified, investigator-designated target knee with most pain
- **Unilateral Symptomatic without Widespread Pain (UNI WP-, n=128):**
  - excludes subjects with comorbid pain
  - post-hoc, Unilateral Symptomatic **excluding** subjects with Widespread Pain Index > 4 and Symptom Severity > 2
- **KL grade:** Non-target knee ≥ target knee in 91% of subjects
  - KL distribution between unilateral and bilateral symptomatic subjects similar
- **Multiple imputation for missing data**
WOMAC Pain [0-50]
Actual scores (mean)

ITT
Unilateral Symptomatic
Unilateral Symptomatic without Widespread Pain

*P<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO
WOMAC Function [0-170]
Actual scores (mean)

ITT
- SM04690 0.03 mg (N=112)
- SM04690 0.07 mg (N=117)
- SM04690 0.23 mg (N=110)
- Placebo (N=116)

Unilateral Symptomatic
- SM04690 0.03 mg (N=45)
- SM04690 0.07 mg (N=35)
- SM04690 0.23 mg (N=45)
- Placebo (N=39)

Unilateral Symptomatic without Widespread Pain
- SM04690 0.03 mg (N=34)
- SM04690 0.07 mg (N=29)
- SM04690 0.23 mg (N=33)
- Placebo (N=32)

*P<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO
WOMAC A1 Pain [0-10]
Actual scores (mean)

ITT

Unilateral Symptomatic

Unilateral Symptomatic without Widespread Pain

*P<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO
SM04690 0.07 mg average (scaled) improvement over PBO

<table>
<thead>
<tr>
<th></th>
<th>WOMAC Pain [0-10]</th>
<th>WOMAC Function [0-10]</th>
<th>WOMAC A1 [0-10]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT</td>
<td>UNI</td>
<td>UNI WP-</td>
</tr>
<tr>
<td>Week 13</td>
<td>0.14</td>
<td>0.16</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 26</td>
<td>0.30</td>
<td>0.92</td>
<td><strong>0.92</strong></td>
</tr>
<tr>
<td>Week 39</td>
<td>0.36</td>
<td>1.18</td>
<td><strong>1.18</strong></td>
</tr>
<tr>
<td>Week 52</td>
<td>0.24</td>
<td><strong>1.12</strong></td>
<td><strong>1.12</strong></td>
</tr>
</tbody>
</table>

*Improvement is absolute value of 0.07 mg treatment effect over PBO from a baseline adjusted ANCOVA.
Statistically significant $P<0.05$.  

13
SM04690 0.07 mg effect size versus PBO at Week 52: Unilateral Symptomatic without Widespread Pain subjects

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Improvement</th>
<th>Mean Square Error</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC A1</td>
<td>1.4</td>
<td>3.4</td>
<td>0.764</td>
</tr>
<tr>
<td>WOMAC Pain</td>
<td>5.9</td>
<td>81.7</td>
<td>0.655</td>
</tr>
<tr>
<td>WOMAC Physical Function</td>
<td>24.7</td>
<td>1061.0</td>
<td>0.757</td>
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</tbody>
</table>
This post-hoc analysis of SM04690 0.07 mg and WOMAC A1

Supports a previous study assessing WOMAC signal and aggregate score responsiveness\(^1\)

At 52 weeks compared with PBO, Unilateral Symptomatic with and without Widespread Pain subgroups demonstrated significant WOMAC A1 pain improvements, corresponding with significant WOMAC Pain and Function improvements

In the Unilateral Symptomatic without Widespread Pain subgroup, effect size comparisons among WOMAC A1, Pain, and Function subscores at Week 52 were similar, supporting the responsiveness of the A1 question

Thank you

Samumed posters:
SM04690-OA-02 52-Week Data – SAT0586
SM04755 Tendinopathy – THU0522
SM04755 Psoriasis – THU0046
SM04690-OA-02 Radiographic Outcomes – FRI0534
Meta-Analysis: Intra-Articular Saline Control – FRI0542
SM04690 Preclinical OA – FRI0552
Intra-Articular Placebo Effect in Knee OA Therapies – SAT0565