RESULTS FROM A 52 WEEK RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF A NOVEL, INTRA-ARTICULAR, WNT PATHWAY INHIBITOR (SM04690) FOR THE TREATMENT OF KNEE OSTEOARTHRITIS

Yusuf Yazici, Timothy E. McAlindon, Allan Gibofsky, Nancy E. Lane, Daniel J. Clauw, Eddie Armas, Nebojsa Skrepnik, Christopher J. Swearingen, Anita DiFrancesco, Jeymi R. Tambiah, and Marc C. Hochberg
Disclosures

- **Y. Yazici**: Samumed, LLC; salary and equity
- **T. McAlindon**: Samumed, LLC, grant/research support; Astellas, Flexion, Pfizer, Regeneron, Samumed, LLC, and Seikugaku, consulting
- **A. Gibofsky**: AbbVie, Amgen, Johnson & Johnson, GSK, Regeneron, shareholder; AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, LLC, consulting; AbbVie, Celgene, Pfizer, speakers bureau
- **N. Lane**: Samumed, LLC, consulting
- **D. Clauw**: AbbVie, Astellas, Cerephex, Eli Lillly, Forest Laboratories, Johnson and Johnson, Merck, Pfizer, Purdue, Samumed, LLC, Theravance, Tonix, UCB, Williams and Connolly LLP, Zynerba, consulting
- **N. Skrepnik**: Samumed, LLC, grant/research support; Orthofix and Sanofi, consulting
- **E. Armas**: Samumed, LLC, grant/research support
- **C. Swearingen**: Samumed, LLC; salary and equity
- **A. DiFrancesco**: Samumed, LLC; salary and equity
- **J. Tambiah**: Samumed, LLC; salary and equity
- **M. Hochberg**: Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Samumed, LLC, Theralogix LLC, consulting
Osteoarthritis (OA)

- The most common form of arthritis
  - Affects over 250 million persons worldwide\(^1\)
  - Knee OA has a global prevalence of 3.8%\(^2\)
- Accounts for more functional limitation, work loss and physical disability than any other chronic disease\(^1,3\)
- Most common indication for total joint arthroplasty\(^3\)
- Associated with excess mortality due to cardiovascular disease\(^4\)
- Multiple risk factors: age, BMI, joint injury, occupation, genetics\(^5\)

Wnt signaling pathway and OA

• Wnt proteins are over-expressed and more active in OA joints\(^1\)\(^-\)\(^2\)
• Wnt pathway mutations (e.g. FrzB, DOT1L) are associated with OA\(^3\)\(^-\)\(^4\)
• Wnt signaling is involved in increased bone formation and cartilage breakdown
• Progenitor cells reside in the synovium and subchondral bone\(^5\)\(^-\)\(^7\)

Hypothesis: Inhibiting the Wnt Pathway protects and regenerates cartilage


Figure adaptations: www.york.ac.uk and Bush J & Beier F. 2013. Nature Med.
SM04690: A proposed treatment for knee OA

- A small molecule, intra-articular, Wnt pathway inhibitor in development for the treatment of knee OA\(^1,2\)
- In preclinical studies, inhibited inflammation, decreased cartilage degradation, and regenerated cartilage\(^1\)
- In preclinical studies, demonstrated sustained local exposure and no observable systemic toxicity\(^1,2\)
- Previous phase 1 study suggested a single intra-articular SM04690 injection appeared well-tolerated and showed potential for improving symptoms and maintaining joint space width in knee OA subjects\(^2\)

1. Deshmukh V, et al. (2017) OAC.
**Primary objective:** Change from baseline in WOMAC pain at Week 13

- **Clinical Assessments:** WOMAC Function, Pain; Patient and MD Global Assessment; SF-36
- **Imaging:** Knee X-ray
- **Safety Assessments:** Adverse Events (AEs), Vital signs, Physical exam, Lab panels
### SM04690-OA-02: Radiographic methodology

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Lin’s Concordance Coeff.</th>
<th>Difference (mm)</th>
<th>BA LOA$^1$ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>431 Intra-observer$^2$</td>
<td>64</td>
<td>0.92</td>
<td>0.13 ± 0.35</td>
<td>-0.56 to 0.83</td>
</tr>
<tr>
<td>431 Inter-observer$^2$</td>
<td>64</td>
<td>0.90</td>
<td>0.04 ± 0.42</td>
<td>-0.78 to 0.86</td>
</tr>
<tr>
<td>OAI Inter-observer$^3$</td>
<td>63</td>
<td>0.96</td>
<td>-0.05 ± 0.27</td>
<td>-0.58 to 0.48</td>
</tr>
</tbody>
</table>

- Images obtained using QuAP™ positioner, centrally read in 72 hours
- Mean baseline KL Grade 2 in OAI, KL Grade 3 in SM04690-OA-02
- Radiographic JSN remains current ‘gold standard’ for assessing disease modification in OA$^4$-$^7$
- Radiographic changes >0.13 mm represent actual or true change in JSN$^8$
- Knee OA natural history of JSN rate is 0.18-0.47 mm/year$^9$
- Worsening pain and function occur in tandem with radiographic progression$^{10}$

1. Bland-Altman’s Limits of Agreement
2. Using QMA® technique for JSN
3. Using Osteoarthritis Initiative (OAI) protocol for JSN measurements
5. Reginster et al. (2015) OAC.
7. EMA guideline on clin invest in OA 2010.
10. Riddle and Juranek (2015) OAC.
<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-80 years</td>
<td>BMI &gt;40</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>
</tr>
<tr>
<td></td>
<td>Hyaluronic acid within 6 months</td>
</tr>
<tr>
<td></td>
<td>Acupuncture within 1 month</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>Pain VAS score of 30-80 for target knee</td>
<td>Any chronic condition not well controlled &gt;3 months</td>
</tr>
</tbody>
</table>
SM04690-OA-02: Patient disposition

1033 subjects screened

578 subjects discontinued prior to randomization

455 subjects randomized

3 subjects discontinued prior to treatment

0.03 mg SM04690
112 subjects
- Discontinued: AE: n=1
- Lost to follow up: n=2
- Subject withdrawals: n=4
- Other: n=2

0.07 mg SM04690
117 subjects
- Discontinued: AE: n=3
- Lost to follow up: n=1
- Subject withdrawals: n=3
- Other: n=3

0.23 mg SM04690
109 subjects
- Discontinued: AE: n=4
- Lost to follow up: n=2
- Subject withdrawals: n=5
- Other: n=3

PBO
114 subjects
- Discontinued: AE: n=1
- Lost to follow up: n=2
- Subject withdrawals: n=11
- Other: n=3
### SM04690-OA-02: Demographics

(ITT analysis set)

<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 at Consent (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>Race [n(%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>92 (82.1%)</td>
<td>102 (87.2%)</td>
<td>96 (87.3%)</td>
<td>102 (87.9%)</td>
<td>392 (86.2%)</td>
</tr>
<tr>
<td>African-American</td>
<td>18 (16.1%)</td>
<td>14 (12.0%)</td>
<td>12 (10.9%)</td>
<td>10 (8.6%)</td>
<td>54 (11.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.9%)</td>
<td>0</td>
<td>2 (1.8%)</td>
<td>0</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td><strong>Kellgren-Lawrence 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 OA [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>
</tbody>
</table>
**Incidence of AEs**  
*(Safety analysis set)*

<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 / 3 (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>

<table>
<thead>
<tr>
<th>0.03 mg (n=111)</th>
<th>0.07 mg (n=114)</th>
<th>0.23 mg (n=104)</th>
<th>Placebo (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Reporting AE(s) [N(%)]</td>
<td>61 (55.0)</td>
<td>65 (57.0)</td>
<td>47 (45.2)</td>
</tr>
<tr>
<td>Subjects Reporting No AE(s) [N(%)]</td>
<td>50 (45.0)</td>
<td>49 (43.0)</td>
<td>57 (54.8)</td>
</tr>
<tr>
<td>Subjects Reporting SAE(s) [#AE / N(%)</td>
<td>7/5 (4.5)</td>
<td>12/4 (3.5)</td>
<td>5/4 (3.8)</td>
</tr>
</tbody>
</table>

No SAEs were deemed related to study drug by PI.

*All AEs deemed related to drug per protocol.*
SM04690-OA-02: Analysis groups

- Intention-to-treat population (ITT, n=455): all randomized subjects
- ‘Unilateral symptomatic’ population (n=164):
  - Pre-specified, investigator designated ‘target knee’ as knee with most pain
  - Determined per protocol on patient history and examination
  - Contralateral knee pain threshold not limited at enrollment
- ‘Unilateral symptomatic without widespread pain’ population (n=128):
  - Post-hoc, unilateral symptomatic as above plus:
  - Widespread Pain Index score ≤ 4 and Symptom Severity score ≤ 2
- Missing data were imputed using multiple imputation
- KL grade: Non-target knee equal or worse than target knee in 91% of subjects (n=386 of 424 non-target KLs)
  - KL grades were equivalent between unilateral symptomatic and bilateral symptomatic subjects
WOMAC Pain [0-50]
Actual scores (mean)

ITT

Unilateral Symptomatic

Unilateral Symptomatic without Widespread Pain

0 4 13 26 39 52
0 4 13 26 39 52
0 4 13 26 39 52
WOMAC Pain (0-50)
WOMAC Pain (0-50)
WOMAC Pain (0-50)
(ITT imputed)
(ITT imputed)
(ITT imputed)
Time (weeks)
Time (weeks)
Time (weeks)

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

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

SM04690 0.03 mg (N=34)
SM04690 0.07 mg (N=29)
SM04690 0.23 mg (N=33)
Placebo (N=32)
WOMAC Pain [0-50]
Ladder plots comparing mean (± 95%CI) to placebo

WOMAC Function [0-170]
Actual scores (mean)

ITT
Unilateral Symptomatic
Unilateral Symptomatic without Widespread Pain
WOMAC Function [0-170]
Ladder plots comparing mean (± 95%CI) to placebo

Intra- and inter-observer reproducibility 0.92 & 0.90 respectively. QuAP™ positioner used. Centrally, blinded read.
Medial joint space width (mm)
Ladder plots comparing mean (± 95%CI) to placebo

Comparisons from Baseline-adjusted ANCOVA versus Placebo. §MDD: Minimal Detectable Difference defined as 0.13 mm of medial joint space width. Dupuis, et al. (2003) OAC.
mJSW change concordance with WOMAC Pain and Function response (post-hoc analysis)
mJŚW change concordance with WOMAC Pain and Function
Outcomes measured at Week 52

Pain and Function response defined as having both Pain and Function responses separately. Baseline mJSW-adjusted logistic regression used to estimate concordance.
Discussion

This proof-of-concept study:

• Did not meet its primary objective for the ITT population
• Identified a potential therapeutic dose, 0.07 mg SM04690
• Identified a potential target population
  – Unilateral symptomatic knee OA subjects without widespread pain discriminate target knee WOMAC outcomes better than bilateral symptomatic subjects and those with widespread pain
  – We hypothesize that when the target knee in an unilateral symptomatic subject was injected, biomechanical load was normalized between both knees. In bilateral symptomatic subjects, after the target knee was injected (and on average improved), it gained increased biomechanical loading as the non-treated knee remained painful
  – We hypothesize that the relatively unloaded unilateral symptomatic knee provided an enhanced environment for SM04690 to improve cartilage degradation and regeneration over PBO

• Study limitations included no formal sample size estimation and small subgroups

Summary

This phase 2 trial demonstrated:
- SM04690 appeared safe and well-tolerated
- Clinically meaningful improvements in WOMAC Pain and Function for all subjects at all time points compared to baseline
- Pain, function, and radiographic improvements compared to PBO were observed in 0.07 mg SM04690 Unilateral Symptomatic and Unilateral Symptomatic without Widespread Pain subjects
- Additional analyses presented Monday, 9-11 AM:
  - Poster #1201: Reducing Heterogeneity in OA Clinical Trials
  - Poster #1204: Radiographic Outcomes Were Associated with Pain and Function Responses
- Innovation Theater, Monday 3:30-4:15, Exhibit Hall Theater B

A Phase 2b study to confirm target population and dose is ongoing (NCT03122860)
SM04690 OA clinical program

• SM04690-OA-01, Phase 1, N=61 (completed)
  - 24 weeks, safety with exploratory efficacy
• SM04690-OA-02, Phase 2, N=455 (completed)
  - 52 weeks, primary endpoint 13 week WOMAC pain
• SM04690-OA-04, Phase 2, N=700 (enrollment complete)
  - 24 weeks, primary endpoints 24 week S&S and JSW
  - Started April 2017, data available May 2018
• SM04690-OA-05, safety extension (observational with no additional injections; ongoing)
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC
• SM04690-OA-08, MRI, N=15
  - 52 weeks, exploratory evaluation of cartilage quality and thickness
  - Estimated November 2017 start
Thank you