SM04690: Potential first-in-class disease modifying treatment for knee osteoarthritis

Nancy Lane, MD
## Disclosures

<table>
<thead>
<tr>
<th>Name</th>
<th>Disclosures</th>
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</thead>
<tbody>
<tr>
<td>Yusuf Yazici</td>
<td>Samumed, LLC, employee and shareholder</td>
</tr>
<tr>
<td>Timothy McAlindon</td>
<td>Samumed, LLC, Astellas, Flexion, Pfizer, Regeneron, Seikagaku</td>
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<tr>
<td>Allan Gibofsky</td>
<td>AbbVie, Amgen, Johnson &amp; Johnson, GSK, Regeneron, Pfizer, Horizon Iroko, Celgene, Novartis/Sandoz, Samumed, LLC</td>
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<tr>
<td>Nancy Lane</td>
<td>Samumed, LLC</td>
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<tr>
<td>Daniel Clauw</td>
<td>AbbVie, Astellas, Cerephex, Eli Lilly, Forest Laboratories, Johnson &amp; Johnson, Merck, Pfizer, Purdue, Theravance, Tonix, UCB, Williams and Connolly LLP, Zynerba, Samumed, LLC</td>
</tr>
<tr>
<td>Christopher Swearingen</td>
<td>Samumed, LLC, employee and shareholder</td>
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<tr>
<td>Anita DiFrancesco</td>
<td>Samumed, LLC, employee and shareholder</td>
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<td>Jeyanesh Tambiah</td>
<td>Samumed, LLC, employee and shareholder</td>
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<tr>
<td>Marc Hochberg</td>
<td>Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Theralogix, LLC, Samumed, LLC</td>
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Knee osteoarthritis (OA), the Wnt pathway, and SM04690

• The Wnt pathway is upregulated in OA.\(^1,2\) Inhibition may regenerate and protect articular cartilage.
• SM04690 is a small-molecule Wnt pathway inhibitor for potential treatment of knee OA. In preclinical studies:
  – Inhibited inflammation and cartilage degradation\(^3\)
  – Regenerated cartilage\(^3\)
  – Demonstrated sustained local exposure and no systemic toxicity\(^3,4\)
• A phase 1 study suggested a single SM04690 injection had potential for improving symptoms and maintaining joint space in knee OA subjects\(^4\)
• Results from a 52-week, phase 2a study are presented

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 for medial joint space width (mJSW)

Safety assessments: Adverse events (AEs), vital signs, physical exam, lab panels
## Key inclusion / exclusion criteria

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<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 Hyaluronic acid within 6 months 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>
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</tbody>
</table>
SM04690 Phase 2a: Study participant flow chart

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

Placebo
114 subjects

Discontinued:
AE: n=1
Lost to follow up: n=2
Subject withdrawals: n=11
Other: n=3
### SM04690 Phase 2a: Study subject characteristics (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>N</td>
<td>112</td>
<td>117</td>
<td>110</td>
<td>116</td>
<td>455</td>
</tr>
<tr>
<td>Age at consent (years) [mean (SD)]</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>BMI (kg/m²) [mean (SD)]</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>Female [n(%)]</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>Race [n(%)]</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>Kellgren-Lawrence grade 3 [n(%)]</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>Unilateral symptomatic OA [n(%)]</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 / 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>

<table>
<thead>
<tr>
<th></th>
<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>
<td>53 (49.1)</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>
<td>55 (50.9)</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>
<td>3/3 (2.8)</td>
</tr>
</tbody>
</table>

No SAEs were deemed related to study drug by PI.

*All AEs deemed related to drug per protocol.
• **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
Comparisons from baseline-adjusted ANCOVA versus placebo. †MCID: Minimal clinically important difference defined as 10% (5 points) of WOMAC Pain subscore.

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) with placebo

Comparisons from baseline-adjusted ANCOVA versus placebo. ‡MCID: Minimal clinically important difference defined as 10% (17 points) of WOMAC Function subscore.

Medial Joint Space Width (mJSW) (mm)
Actual measurements (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)

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) with placebo

Comparisons from baseline-adjusted ANCOVA versus placebo. §MDD: Minimal detectable difference defined as 0.13 mm of mJSW.

Dupuis, et al. (2003) OAC.
This proof-of-concept study

• Did not meet primary objective for ITT population

• Identified a potential target population
  – UNI subjects probably discriminated target knee WOMAC outcomes better than bilateral symptomatic subjects\(^1\)
  – We hypothesize treated, relatively unloaded UNI knees provided enhanced environment for SM04690 to improve cartilage regeneration\(^2,3\)

• Identified a potential therapeutic dose, SM04690 0.07 mg
  – Non-linear dose response observed

• Study limitations: Study was not powered to analyze subgroups

Conclusions

• SM04690 appeared safe and well-tolerated
• Clinically meaningful improvements in WOMAC Pain and Function observed for all subjects at all time points vs. baseline
• In this proof-of-concept study, a potential therapeutic dose (0.07mg) and target population were identified
  – Pain, function, and radiographic improvements compared with placebo were observed in 0.07 mg SM04690 Unilateral Symptomatic and Unilateral Symptomatic without Widespread Pain subjects at Week 52
Long-term extension data
ITT (As Observed, through 18 months)
Comparison of enrollees vs non-enrollees in long-term extension

• Phase 2a subjects were enrolled into an open label long-term (5 year) extension study

• Similar demographic data between enrollees and non-enrollees
  – Age ~60, BMI ~29, ~56% female

• Similar OA features between enrollees and non-enrollees
  – ~65% Kellgren-Lawrence grade 3, ~35% Unilateral Symptomatic

• Similar baseline data between enrollees and non-enrollees
  – WOMAC Pain ~52, WOMAC Function ~55, medial JSW ~3.3 mm

• Enrollees improved ~5 points more than non-enrollees on both WOMAC Pain and Function observed in the full Phase 2a population
WOMAC Pain [0-100]
ITT (As Observed)

Actual values

Change from baseline

Compared to PBO

0.03 mg
Favors Placebo
Favors SM04690

-1.83
3.11

0.07 mg

3.03

0.23 mg

0.39

0.39

-1.90
Medial Joint Space Width (mm)

**ITT (As Observed)**

**Actual values**

**Change from baseline**

**Compared to PBO**

- **0.03 mg**
  - Favors Placebo: 0.13
  - Favors SM04690: 0.09

- **0.07 mg**
  - Favors Placebo: 0.10
  - Favors SM04690: 0.06

- **0.23 mg**
  - Favors Placebo: 0.02
  - Favors SM04690: 0.17

P=0.036

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Long-term extension data
Unilateral Symptomatic without Widespread Pain, (As Observed, through 18 months)
WOMAC Pain [0-100]
Unilateral Symptomatic without Widespread Pain

Actual values

Change from baseline

Compared to PBO

Unilateral Symptomatic without Widespread Pain

- SM04690 0.03 mg
- SM04690 0.07 mg
- SM04600 0.23 mg
- Placebo

Favors Placebo
Favors SM04690

0.03 mg

- Month 6: 7.01
- Month 12: 6.53
- Month 18: 9.42
- Month 24: 11.85

P=0.04

0.07 mg

- Month 6: 9.34
- Month 12: 3.84
- Month 18: 2.50
- Month 24: 10.20

P=0.048

0.23 mg

- Month 6: 1.12
- Month 12: 2.50
- Month 18: 10.20
- Month 24: 11.85
Medial Joint Space Width (mm)
Unilateral Symptomatic without Widespread Pain

Actual values

Change from baseline

Compared to PBO

Unilateral Symptomatic without Widespread Pain

- SM04690 0.03 mg
- SM04690 0.07 mg
- SM04600 0.23 mg
- Placebo
SM04690 OA status of clinical development program

- SM04690-OA-04, phase 2b, N=695 (completed, NCT03122860)
  - 24 week single injection, primary endpoints 24 week S&S and JSW
  - Data available fall 2018

- SM04690-OA-05, safety extension (observational with no additional injections, NCT02951026)
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC

- SM04690-OA-06, phase 2, bone health, N=100
  - 52 week two injections, knee qCT, DXA spine/hip, bone health biomarkers
  - Estimated September 2018 start

- SM04690-OA-08, MRI, N=15
  - 52 week single injection, exploratory evaluation of cartilage quality and thickness
  - Estimated October 2018 start
Thank you